From: **Effects of Iron Isomaltoside vs Ferric Carboxymaltose on Hypophosphatemia in Iron-Deficiency Anemia: Two Randomized Clinical Trials**

JAMA. 2020;323(5):432-443. doi:10.1001/jama.2019.22450

JAMA Network

QUESTION What are the risks of hypophosphatemia following iron replacement with iron isomaltoside 1000/ferric derisomaltose vs ferric carboxymaltose?

CONCLUSION These randomized trials found that in patients with iron-deficiency anemia, iron isomaltoside, vs ferric carboxymaltose, resulted in lower incidence of hypophosphatemia, but further research is needed to determine the clinical importance of these findings.

POPULATION

230 Women
12 Men

Adults aged >18 years with iron-deficiency anemia and intolerance or unresponsiveness to ≥1 month of oral iron

Mean age: 44 years

LOCATIONS

30 Outpatient clinics in the United States

INTERVENTION

123 Patients analyzed in trial A
122 Patients analyzed in trial B

62 Patients in trial A
61 Patients in trial B

Iron isomaltoside
Intravenous administration of iron isomaltoside, 1000 mg, on day 0

61 Patients in trial A
61 Patients in trial B

Ferric carboxymaltose
Intravenous administration of ferric carboxymaltose, 750 mg, infused on days 0 and 7

PRIMARY OUTCOME

Incidence of hypophosphatemia (serum phosphate level <2.0 mg/dL)

FINDINGS

© AMA

Incidence of hypophosphatemia

Trial A

Iron isomaltoside	Ferric carboxymaltose
7.9%	75.0%

Trial B

Iron isomaltoside	Ferric carboxymaltose
8.1%	73.7%

Adjusted rate difference:

Trial A: −67.0% (95% CI, −77.4% to −51.5%)

Trial B: −65.8% (95% CI, −76.6% to −49.8%)

Wolf M, Rubin J, Achebe M, et al. Effects of iron isomaltoside vs ferric carboxymaltose on hypophosphatemia in iron-deficiency anemia: two randomized clinical trials [published February 4, 2020]. *JAMA*. doi:10.1001/jama.2019.22450

Figure Legend:

Effects of Iron Isomaltoside vs Ferric Carboxymaltose on Hypophosphatemia in Iron-Deficiency Anemia

JAMA | Original Investigation

Effects of Iron Isomaltoside vs Ferric Carboxymaltose on Hypophosphatemia in Iron-Deficiency Anemia
Two Randomized Clinical Trials

Myles Wolf, MD, MMSc; Janet Rubin, MD; Maureen Achebe, MD; Michael J. Econs, MD; Munro Peacock, MD; Erik A. Imel, MD; Lars L. Thomsen, MD; Thomas O. Carpenter, MD; Thomas Weber, MD; Vincent Brandenburg, MD; Heinz Zoller, MD

IMPORTANCE Intravenous iron enables rapid correction of iron-deficiency anemia, but certain formulations induce fibroblast growth factor 23–mediated hypophosphatemia.

OBJECTIVE To compare risks of hypophosphatemia and effects on biomarkers of mineral and bone homeostasis of intravenous iron isomaltoside (now known as ferric derisomaltose) vs ferric carboxymaltose.

DESIGN, SETTING, AND PARTICIPANTS Between October 2017 and June 2018, 245 patients aged 18 years and older with iron-deficiency anemia (hemoglobin level ≤11 g/dL; serum ferritin level ≤100 ng/mL) and intolerance or unresponsiveness to 1 month or more of oral iron were recruited from 30 outpatient clinic sites in the United States into 2 identically designed, open-label, randomized clinical trials. Patients with reduced kidney function were excluded. Serum phosphate and 12 additional biomarkers of mineral and bone homeostasis were measured on days 0, 1, 7, 8, 14, 21, and 35. The date of final follow-up was June 19, 2018, for trial A and May 29, 2018, for trial B.

INTERVENTIONS Intravenous administration of iron isomaltoside, 1000 mg, on day 0 or ferric carboxymaltose, 750 mg, infused on days 0 and 7.

MAIN OUTCOMES AND MEASURES The primary end point was the incidence of hypophosphatemia (serum phosphate level <2.0 mg/dL) between baseline and day 35.

RESULTS In trial A, 123 patients were randomized (mean [SD] age, 45.1 [11.0] years; 95.9% women), including 62 to iron isomaltoside and 61 to ferric carboxymaltose; 95.1% completed the trial. In trial B, 122 patients were randomized (mean [SD] age, 42.6 [12.2] years; 94.1% women), including 61 to iron isomaltoside and 61 to ferric carboxymaltose; 93.4% completed the trial. The incidence of hypophosphatemia was significantly lower following iron isomaltoside vs ferric carboxymaltose (trial A: 7.9% vs 75.0% [adjusted rate difference, −67.0% {95% CI, −77.4% to −51.5%}], $P < .001$; trial B: 8.1% vs 73.7% [adjusted rate difference, −65.8% {95% CI, −76.6% to −49.8%}], $P < .001$). Beyond hypophosphatemia and increased parathyroid hormone, the most common adverse drug reactions (No./total No.) were nausea (iron isomaltoside: 1/125; ferric carboxymaltose: 8/117) and headache (iron isomaltoside: 4/125; ferric carboxymaltose: 5/117).

CONCLUSIONS AND RELEVANCE In 2 randomized trials of patients with iron-deficiency anemia who were intolerant of or unresponsive to oral iron, iron isomaltoside (now called ferric derisomaltose), compared with ferric carboxymaltose, resulted in lower incidence of hypophosphatemia over 35 days. However, further research is needed to determine the clinical importance of this difference.

TRIAL REGISTRATION ClinicalTrials.gov Identifiers: NCT03238911 and NCT03237065

Visual Abstract

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Myles Wolf, MD, MMSc, Duke University School of Medicine, 2 Genome Ct, Room 1009, Durham, NC 27710 (myles.wolf@duke.edu).

JAMA. 2020;323(5):432-443. doi:10.1001/jama.2019.22450

Iron-deficiency anemia is a global health problem.[1,2] Iron isomaltoside 1000 (now known as ferric derisomaltose) and ferric carboxymaltose are intravenous iron formulations that were developed to rapidly correct iron-deficiency anemia, especially in patients who do not tolerate or fail to respond to oral iron.[3,4] Both iron isomaltoside and ferric carboxymaltose effectively correct iron-deficiency anemia, but their safety profiles differ.[5-8] Several studies have reported that ferric carboxymaltose causes high rates of hypophosphatemia by acutely increasing circulating concentrations of full-length, biologically active fibroblast growth factor 23, which causes hypophosphatemia by stimulating urinary phosphate excretion and reducing serum 1,25-dihydroxyvitamin D levels.[9-11] Severe hypophosphatemia can cause serious complications, including rhabdomyolysis, heart failure, and respiratory failure, and chronic hypophosphatemia can be complicated by osteomalacia and fractures.[12,13]

Previous clinical trials suggested that the risk of hypophosphatemia may be lower with iron isomaltoside than with ferric carboxymaltose,[5,7,8,14,15] but data from randomized trials that directly compared the 2 formulations are limited. Furthermore, no controlled studies have systematically investigated the effects of any intravenous iron on biomarkers of bone metabolism to link intravenous iron-associated changes in mineral metabolism to the skeletal complications described in case reports.[13] Two randomized clinical trials were conducted to compare the incidence, severity and mechanisms of hypophosphatemia, and effects on biochemical biomarkers of mineral and bone homeostasis of treatment with iron isomaltoside (called ferric derisomaltose by the US Food and Drug Administration as of June 2019) or ferric carboxymaltose in patients with iron-deficiency anemia.

Key Points

Question What are the risks of hypophosphatemia following iron replacement with iron isomaltoside 1000 (now called ferric derisomaltose) vs ferric carboxymaltose?

Findings In 2 randomized trials of 245 total patients (trial A: n = 123; trial B: n = 122) with iron-deficiency anemia, who were intolerant to or unresponsive to oral iron, the incidence of hypophosphatemia with use of iron isomaltoside, compared with ferric carboxymaltose, was 7.9% vs 75.0% in trial A and 8.1% vs 73.7% in trial B over 35 days; both differences were statistically significant.

Meaning Iron isomaltoside, compared with ferric carboxymaltose, resulted in lower incidence of hypophosphatemia, but further research is needed to determine the clinical importance of these findings.

Methods

Trial Design

Two identically designed, open-label, randomized clinical trials were conducted at 30 sites across the United States between October 2017 and June 2018 (trial A) and October 2017 and May 2018 (trial B). The date of final follow-up was June 19, 2018, for trial A and May 29, 2018, for trial B. Trial protocols are available in Supplement 1 and Supplement 2, with revisions documented in eTable 1 in Supplement 3. These trials were conducted to support the US Food and Drug Administration submission package and the intended label of iron isomaltoside. Iron isomaltoside 1000 is also known as ferric derisomaltose. Iron isomaltoside 1000 is the generic name initially approved in the European Union, whereas ferric derisomaltose is the international nonproprietary name and United States Adopted Name. Two individually powered studies were performed in line with general regulatory recommendations to better demonstrate the robustness of results while decreasing the risk of findings occurring by chance. In both trials, a screening period was followed by a baseline randomization visit on day 0 and follow-up visits on days 1, 7, 8, 14, 21, and 35. Nonfasting blood and spot urine samples were collected at each visit. The day 1 and day 8 assessments were included to capture physiological responses 24 hours after iron administrations.

The trials were approved by a single institutional review board (Western Institutional Review Board, Puyallup, Washington; 98374-2115) and all patients provided written informed consent.

Patients

Both trials recruited adults aged 18 years and older with iron-deficiency anemia, defined as hemoglobin level of 11 g/dL or less and serum ferritin level of 100 ng/mL or less (to convert to pmol/L, multiply by 2.247), with a history of intolerance or unresponsiveness to 1 month or more of oral iron. Exclusion criteria included body weight less than 50 kg, estimated glomerular filtration rate less than 65 mL/min/1.73 m^2, serum phosphate level less than 2.5 mg/dL, acute bleeding greater than 500 mL within 72 hours before study inclusion, hemochromatosis or other iron-storage disorder, or intravenous iron use within 30 days prior to screening. Additional inclusion and exclusion criteria are presented in eTable 1 in Supplement 3. Race/ethnicity data were collected as part of a comprehensive approach to describing the trials' study populations and because of known differences in bone and mineral metabolism across racial groups. Race and ethnicity were ascertained by patient self-report based on fixed categories (white, black or African American, Asian, Hispanic or Latino, not Hispanic or not Latino, other).

Randomization

Patients were centrally randomized (1:1) using an interactive web response system (IBM Clinical Development eCRF system randomization module) that blinded investigators and patients to assignment to iron isomaltoside or ferric carboxymaltose. Randomization was stratified in blocks of 4 to try to ensure balance across the 2 groups in underlying gynecological cause of iron-deficiency anemia (yes or no) and screening serum phosphate level (<3.5 or ≥3.5 mg/dL).

Interventions

Iron isomaltoside was administered as a single dose of 1000 mg infused over 20 minutes on day 0, according to its anticipated US label. Ferric carboxymaltose was administered at 750 mg on day 0 and 750 mg on day 7, according to its Food and Drug Administration–approved label.[16] The trials were open-label without blinding of the investigational products. During the trials, other forms of iron supplementation, blood transfusion, erythropoiesis-stimulating agents, radiotherapy, and chemotherapy were prohibited.

End Points

The primary end point was the incidence of hypophosphatemia, defined as serum phosphate level less than 2.0 mg/dL, at any time from baseline to day 35. There were multiple secondary safety and efficacy end points (eTable 2 in Supplement 3). Secondary safety end points reported in this article include prevalence of persistent hypophosphatemia at day 35; changes from baseline to each postrandomization visit in biomarkers of mineral and bone homeostasis: serum phosphate, urinary fractional excretion of phosphate, intact fibroblast growth factor 23 (measures only full-length peptide), C-terminal fibroblast growth factor 23 (measures full-length peptide and its C-terminal fragments), 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, 24,25-dihydroxyvitamin D, ionized calcium, and parathyroid hormone (PTH); and number of patients who experienced any adverse drug reactions.

Secondary efficacy end points reported in this article include changes in hemoglobin per gram of iron infused, ferritin, and transferrin saturation from baseline to each postrandomization visit. Post hoc analyses included study site–adjusted analyses of the primary end point, the incidence of severe hypophosphatemia (serum phosphate level ≤1.0 mg/dL) at any time from baseline to day 35, and the prevalence of hypophosphatemia at each postrandomization visit.

Exploratory end points reported in this article include changes in serum biomarkers of bone turnover, including total and bone-specific alkaline phosphatase, N-terminal propeptide of type 1 collagen, carboxy-terminal collagen crosslinks, and changes in hemoglobin level from baseline to each postrandomization visit. A central laboratory that was blinded to randomized treatment performed all laboratory assays, details of which are presented in eTable 3 in Supplement 3.

Sample Size

At the time of protocol development, there was no known minimal clinically important difference in rates of hypophosphatemia between different intravenous iron formulations. Conservatively assuming an incidence of hypophosphatemia of 15% for iron isomaltoside and 40% for ferric carboxymaltose based on prior studies,[9,17-21] each trial required 49 patients in each treatment group to detect a significant difference between groups with 80% power and α of 5%. To account for potential loss to follow-up, 60 patients per treatment group were planned to be randomized in each trial.

Statistical Analysis

The statistical analysis plan is available in Supplement 4. The primary end point and all secondary safety end points were analyzed using the safety data sets, which included all patients who received at least 1 dose of study drug (trial A: iron isomaltoside, n = 63, ferric carboxymaltose, n = 60; trial B: iron isomaltoside, n = 62, ferric carboxymaltose, n = 57). For the secondary efficacy end points, patients were analyzed according to their randomization group (trial A: iron isomaltoside, n = 62, ferric carboxymaltose, n = 61, including 1 patient who erroneously received iron isomaltoside; trial B: iron isomaltoside, n = 61, ferric carboxymaltose, n = 61, including 1 patient who erroneously received iron isomaltoside).

For the primary end point, the difference between the incidence of hypophosphatemia in the iron isomaltoside group vs the ferric carboxymaltose group was calculated using the Cochran-Mantel-Haenszel method with 95% Newcombe CIs,[22] adjusting for randomized strata (and trial, in the pooled analyses of both trials). In a post hoc analysis, the primary end point was analyzed using the Cochran-Mantel-Haenszel method with 95% Newcombe CIs, adjusting for individual study sites. For the patients with no postbaseline measurements (n = 3 across both trials), serum phosphate level was imputed as less than 2.0 mg/dL for the primary analysis. Prevalence of hypophosphatemia at individual time points was analyzed using the same methodology.

Longitudinal changes in biomarkers of bone and mineral homeostasis and in anemia and iron parameters were analyzed using mixed models for repeated measurements with a restricted maximum likelihood–based approach. The models included iron isomaltoside vs ferric carboxymaltose treatment, randomization strata, trial (in the pooled analyses), study day, and treatment-by-day interaction as fixed categorical effects. An unstructured covariance matrix was used to model within-patient error, with baseline values of the continuous dependent variables and baseline value-by-day interaction as fixed covariates. In the mixed-model analyses, patients without postbaseline values had their change from baseline set to zero at the first postbaseline visit. Otherwise, no imputation of missing values was applied.

The numbers of patients who experienced any adverse drug reactions were compared between treatment groups using Fisher exact tests.

Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory.

All statistical analyses were performed using SAS release 9.4 (SAS Institute) and 2-tailed *P* values less than .05 were considered statistically significant.

Results

Of the 554 patients screened across the 2 trials, 123 were randomized to iron isomaltoside and 122 to ferric carboxymaltose;

231 of 245 enrollees completed the trials (**Figure 1**). Demographic and clinical characteristics were well balanced across the treatment groups in both trials (**Table 1**). The 2 trials enrolled mostly women with iron-deficiency anemia due to gynecological bleeding, which is among the most common causes of iron-deficiency anemia.[1] Consistent with the known effects of untreated iron deficiency to stimulate *FGF23* gene transcription and fibroblast growth factor 23 protein cleavage,[11] C-terminal fibroblast growth factor 23 levels were markedly elevated at baseline.

Primary End Point: Incidence of Hypophosphatemia

The incidence of hypophosphatemia at any time from baseline to day 35 was significantly lower among patients treated with iron isomaltoside than with ferric carboxymaltose (trial A: 7.9% vs 75.0% [adjusted rate difference, −67.0% {95% CI, −77.4% to −51.5%}], $P < .001$; trial B: 8.1% vs 73.7% [adjusted rate difference, −65.8% {95% CI, −76.6% to −49.8%}], $P < .001$; **Figure 2**; eTable 4 and eFigure 1 in Supplement 3).

Secondary End Points

Subsequent results of the biomarkers of mineral and bone homeostasis are derived from pooled analyses of trial A and trial B; trial-specific and pooled data for unadjusted and least squares mean changes from baseline are presented in eTable 5 and eTable 6 in Supplement 3.

Serum Phosphate and Urinary Excretion of Phosphate

Beginning at day 1 and through all postbaseline visits, ferric carboxymaltose induced significantly larger magnitude reductions in serum phosphate than iron isomaltoside (**Figure 3** and **Figure 4**; eTable 5 and eFigure 2 in Supplement 3). Urinary phosphate excretion was significantly higher in the ferric carboxymaltose group vs the iron isomaltoside group throughout the study period, with a peak at day 14, which coincided with the ferric carboxymaltose group's nadir of serum phosphate (Figure 3 and Figure 4; eTable 5 and eFigure 2 in Supplement 3).

Fibroblast Growth Factor 23

Within 24 hours after the first dose of ferric carboxymaltose on day 0, mean biologically active intact fibroblast growth factor 23 increased from 46.2 pg/mL to 151.2 pg/mL and reached a peak of 343.6 pg/mL on day 8, which was 24 hours after the second dose of ferric carboxymaltose (Figure 3 and Figure 4; eTable 5 and eFigure 2 in Supplement 3). Thereafter, intact fibroblast growth factor 23 gradually decreased through day 35 in the ferric carboxymaltose group, but remained significantly higher than in the iron isomaltoside group at all postbaseline visits (Figure 3 and Figure 4; eTable 5 and eFigure 2 in Supplement 3). Concentrations of C-terminal fibroblast growth factor 23 declined within 24 hours of either iron isomaltoside or ferric carboxymaltose administration, but increased again in the ferric carboxymaltose group vs the iron isomaltoside group between days 8 and 21, coincident with that group's peak in full-length fibroblast growth factor 23, which is also detected by the C-terminal assay (Figure 3 and Figure 4; eTable 5 and eFigure 2 in Supplement 3).

Vitamin D

Serum concentrations of the storage form of vitamin D, 25-hydroxyvitamin D, remained similar throughout the study in the iron isomaltoside and ferric carboxymaltose groups (eTable 5 in Supplement 3). In contrast, both treatment groups experienced decreases in the biologically active form, 1,25-dihydroxyvitamin D, but the decrease was significantly more pronounced in the ferric carboxymaltose group and persisted throughout the remainder of the study period (Figure 3 and Figure 4; eTable 5 and eFigure 2 in Supplement 3). Serum concentrations of the inactive vitamin D metabolite, 24,25-dihydroxyvitamin D, increased significantly in the ferric carboxymaltose vs the iron isomaltoside group from day 7 onward, and the ferric carboxymaltose group's peak serum 24,25-dihydroxyvitamin D on day 14 coincided with its nadir in 1,25-dihydroxyvitamin D on days 8 to 14 (Figure 3 and Figure 4; eTable 5 and eFigure 2 in Supplement 3).

Calcium and PTH

Compared with iron isomaltoside, levels of ionized calcium decreased significantly on days 7, 8, and 21 in the ferric carboxymaltose group, whereas PTH increased significantly beginning on day 7. From day 14 throughout the duration of the trial, PTH remained significantly higher in the ferric carboxymaltose group (Figure 3 and Figure 4; eTable 5 and eFigure 2 in Supplement 3).

Iron and Anemia Parameters

In trial A and trial B and in the pooled analyses of both trials, iron isomaltoside and ferric carboxymaltose each increased hemoglobin levels, hemoglobin per gram of iron infused, and ferritin and transferrin saturation (eTable 7 and eFigure 3 in Supplement 3).

Exploratory End Points: Bone Turnover Markers

Compared with iron isomaltoside, ferric carboxymaltose induced significant increases in total and bone-specific alkaline phosphatase at multiple postbaseline visits (Figure 3 and Figure 4; eTable 5, eFigure 2, and eFigure 4 in Supplement 3). Compared with iron isomaltoside, ferric carboxymaltose induced significant decreases in N-terminal propeptide of type 1 collagen and carboxy-terminal collagen crosslinks at multiple postbaseline visits (eTable 5 and eFigure 4 in Supplement 3).

Post Hoc End Points and Analyses

The results of post hoc analyses of the primary end point that adjusted for study site were similar to the primary analyses (eTable 4 in Supplement 3).

By day 7 of both trials, the prevalence of hypophosphatemia was significantly lower in patients treated with iron isomaltoside vs ferric carboxymaltose, despite the ferric carboxymaltose group having received only 750 mg of iron by that time vs 1000 mg in the iron isomaltoside group

Figure 1. Participant Flow in Trial A and Trial B Assessing the Effect of Iron Isomaltoside vs Ferric Carboxymaltose on Hypophosphatemia in Patients With Iron-Deficiency Anemia

[a] Some potential study participants had more than 1 reason for exclusion.

[b] One patient randomized to ferric carboxymaltose was erroneously treated with iron isomaltoside and included in the iron isomaltoside safety analysis set.

[c] Three patients randomized to ferric carboxymaltose were not treated and not included in the safety analysis set.

Table 1. Baseline Demographics and Laboratory Parameters

	Trial A		Trial B		Pooled	
	Iron Isomaltoside (n = 63)	Ferric Carboxymaltose (n = 60)	Iron Isomaltoside (n = 62)	Ferric Carboxymaltose (n = 57)	Iron Isomaltoside (n = 125)	Ferric Carboxymaltose (n = 117)
Patient Demographics						
Age, mean (SD), y	43.9 (10.4)	46.3 (11.6)	42.2 (12.9)	43.1 (11.5)	43.0 (11.7)	44.7 (11.6)
Sex, No. (%)						
Female	61 (96.8)	57 (95.0)	58 (93.5)	54 (94.7)	119 (95.2)	111 (94.9)
Male	2 (3.2)	3 (5.0)	4 (6.5)	3 (5.3)	6 (4.8)	6 (5.1)
Race, No. (%)						
White	38 (60.3)	38 (63.3)	28 (45.2)	29 (50.9)	66 (52.8)	67 (57.3)
African American	22 (34.9)	19 (31.7)	32 (51.6)	27 (47.4)	54 (43.2)	46 (39.3)
Asian	2 (3.2)	1 (1.7)	0	0	2 (1.6)	1 (0.9)
Other	1 (1.6)	2 (3.3)	2 (3.2)	1 (1.8)	3 (2.4)	3 (2.6)
Hispanic ethnicity	37 (58.7)	36 (60.0)	23 (37.1)	23 (40.4)	60 (48.0)	59 (50.4)
Weight, mean (SD), kg	80.6 (16.6)	77.4 (20.2)	90.1 (29.2)	84.2 (20.1)	85.3 (24.0)	80.7 (20.3)
BMI, mean (SD)	30.6 (6.1)	29.6 (7.0)	32.3 (8.6)	31.7 (7.9)	31.5 (7.5)	30.7 (7.5)
Gynecological cause of IDA, No. (%)	41 (65.1)	42 (70.0)	44 (71.0)	39 (68.4)	85 (68.0)	81 (69.2)
Laboratory Parameters						
Hemoglobin, mean (SD), g/dL[a,b]	9.8 (1.3)	9.6 (1.3)	9.6 (1.2)	9.3 (1.4)	9.7 (1.3)	9.5 (1.4)
Ferritin, median (IQR), ng/mL[a,c]	6.1 (2.9-12.9)	4.8 (3.1-7.5)	4.8 (2.8-8.7)	5.1 (2.7-8.8)	5.2 (2.8-11.2)	4.8 (3.0-7.7)
Transferrin saturation, median (IQR), %[a,d]	5.6 (3.5-9.7)	4.7 (3.6-7.7)	5.2 (3.5-8.8)	4.8 (3.2-9.2)	5.3 (3.5-9.7)	4.8 (3.4-8.1)
Serum phosphate, mean (SD), mg/dL[e]	3.3 (0.6)	3.3 (0.5)	3.4 (0.5)	3.3 (0.5)	3.4 (0.5)	3.3 (0.5)
Urinary fractional excretion of phosphate, mean (SD), %[f]	11.1 (6.7)	10.3 (4.7)	9.4 (4.9)	10.2 (4.5)	10.3 (5.9)	10.3 (4.6)
C-terminal FGF23, median (IQR), RU/mL[g]	507 (225-1256)	351 (186-857)	579 (162-1317)	454 (89-1344)	539 (196-1257)	398 (142-1192)
Intact FGF23, mean (SD), pg/mL[g]	59.0 (39.8)	46.2 (20.5)	60.9 (50.3)	53.6 (35.3)	59.9 (45.2)	49.9 (29.0)
Ionized calcium, mean (SD), mg/dL[h]	5.1 (0.2)	5.1 (0.2)	5.1 (0.2)	5.1 (0.2)	5.1 (0.2)	5.1 (0.2)
Intact parathyroid hormone, mean (SD), pg/mL[i]	55.1 (26.4)	51.6 (26.4)	55.4 (26.5)	59.9 (33.9)	55.3 (26.3)	55.7 (30.5)
25-Hydroxyvitamin D, mean (SD), ng/mL[j]	23.2 (7.6)	25.9 (7.8)	23.2 (11.0)	23.8 (10.0)	23.2 (9.4)	25.0 (8.9)
1,25-Dihydroxyvitamin D, mean (SD), pg/mL[k]	58.9 (18.2)	63.9 (19.4)	55.6 (16.4)	59.6 (19.6)	57.3 (17.3)	61.8 (19.5)
24,25-Dihydroxyvitamin D, mean (SD), ng/mL[l]	2.1 (1.1)	2.4 (1.2)	2.0 (1.6)	1.9 (1.1)	2.0 (1.4)	2.2 (1.2)
Alkaline phosphatase, mean (SD), IU/L[m]	70.0 (26.9)	72.4 (27.5)	71.8 (18.5)	76.9 (26.8)	70.9 (23.1)	74.6 (27.1)
Bone-specific alkaline phosphatase, mean (SD), µg/L[n]	11.6 (4.1)	12.5 (6.6)	12.0 (3.5)	12.8 (5.9)	11.8 (3.8)	12.7 (6.3)
N-terminal propeptide of type 1 collagen, mean (SD), ng/mL	56.5 (26.3)	57.3 (28.9)	58.4 (25.4)	65.6 (39.4)	57.4 (25.7)	61.4 (34.5)
Carboxy-terminal collagen crosslinks, mean (SD), ng/mL	0.33 (0.16)	0.29 (0.15)	0.33 (0.15)	0.38 (0.22)	0.33 (0.16)	0.34 (0.20)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FGF23, fibroblast growth factor; IDA, iron-deficiency anemia; IQR, interquartile range.

SI conversion factors: To convert alkaline phosphatase to µkat/L, multiply by 0.0167; ferritin to pmol/L, multiply by 2.247; and ionized calcium to mmol/L, multiply by 0.25.

[a] Data are presented for the as-randomized analysis set; all other data in the table are for the safety analysis set.

[b] Reference range: women 18-59 y, 11.6-16.4 g/dL; men 18-59 y, 12.7-18.1 g/dL.

[c] Reference range: women, 11.0-306.8 ng/mL; men, 23.9-336.2 ng/mL.

[d] Calculcated as: (Total serum iron [µmol/L] × 5.586) / (transferrin [g/L] × 100) × 70.9.

[e] Reference range: 2.2-5.1 mg/dL.

[f] Calculcated as: (Urinary phosphate × serum creatinine) / (serum phosphate × urinary creatinine) × 100.

[g] No reference range.

[h] Reference range: 4.6-5.3 mg/dL.

[i] Reference range: 14.0-72.0 pg/mL.

[j] Reference range: 25.0-80.0 ng/mL.

[k] Reference range: 20.8-105.4 pg/mL.

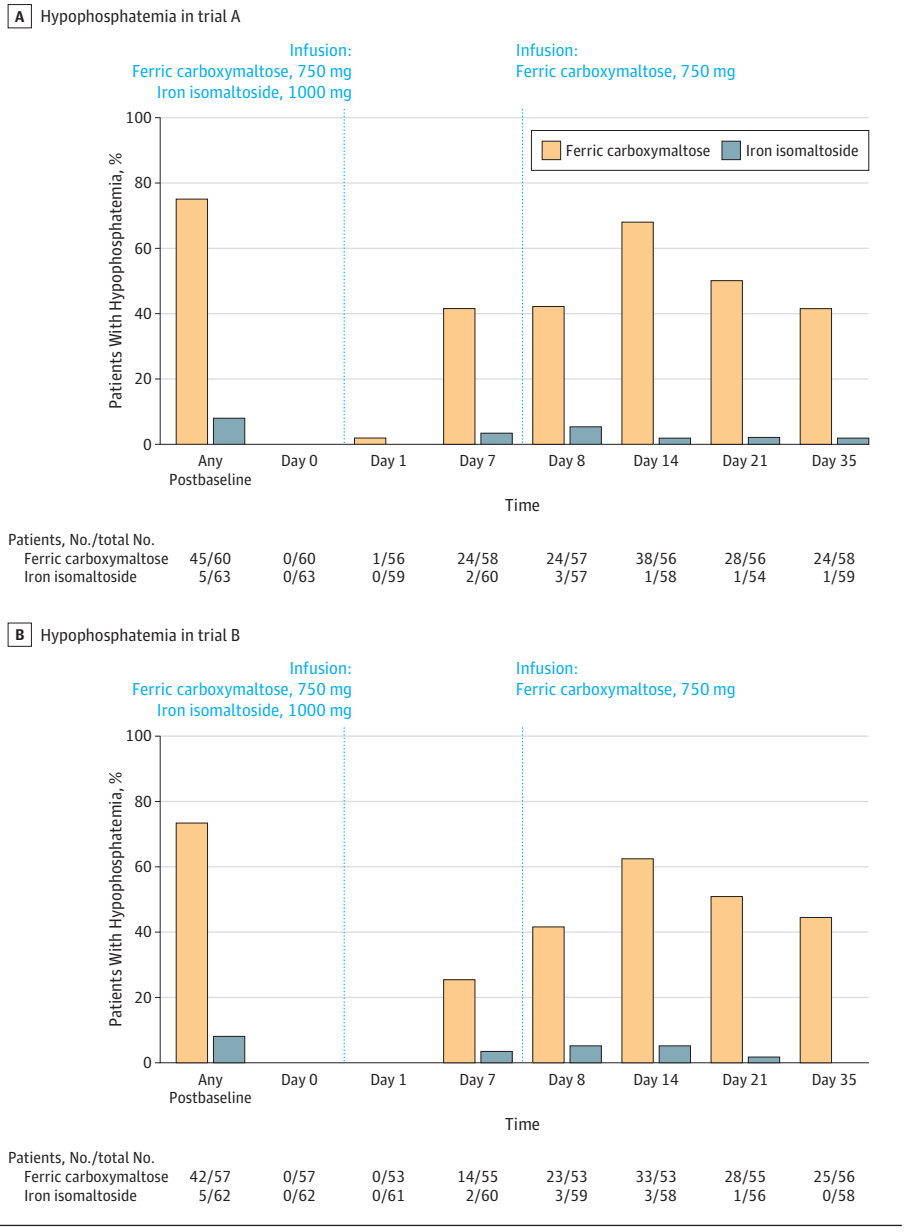
[l] Reference range: 1.6-9.1 ng/mL.

[m] Reference range: women 18-50 y, 31-106 IU/L; women 50-60 y, 35-123 IU/L; men 18-50 y, 31-129 IU/L; and men 50-60 y, 35-131 IU/L.

[n] Reference range: premenopausal women, 2.9-14.5 µg/L; postmenopausal women, 3.8-22.6 µg/L; and men, 3.7-20.9 µg/L.

(Figure 2; eTable 4 in Supplement 3). In both trials, the prevalence of hypophosphatemia peaked on day 14 in the ferric carboxymaltose group (1 week after the second 750-mg dose), and remained significantly higher than in the iron isomaltoside group at study end on day 35 (Figure 2; eTable 4 and eFigure 1 in Supplement 3). Severe hypophosphatemia (serum phosphate ≤1.0 mg/dL) was not observed in iron isomaltoside–treated patients, but developed in 11.3% of ferric carboxymaltose–treated patients in the pooled analysis ($P < .001$).

Figure 2. Hypophosphatemia in Trial A and Trial B



The leftmost columns correspond to the primary outcome of incident hypophosphatemia at any time during the trial. The remaining columns correspond to the proportions of patients with serum phosphate level less than 2.0 mg/dL at each individual time point in the safety analysis set.

Adverse Events

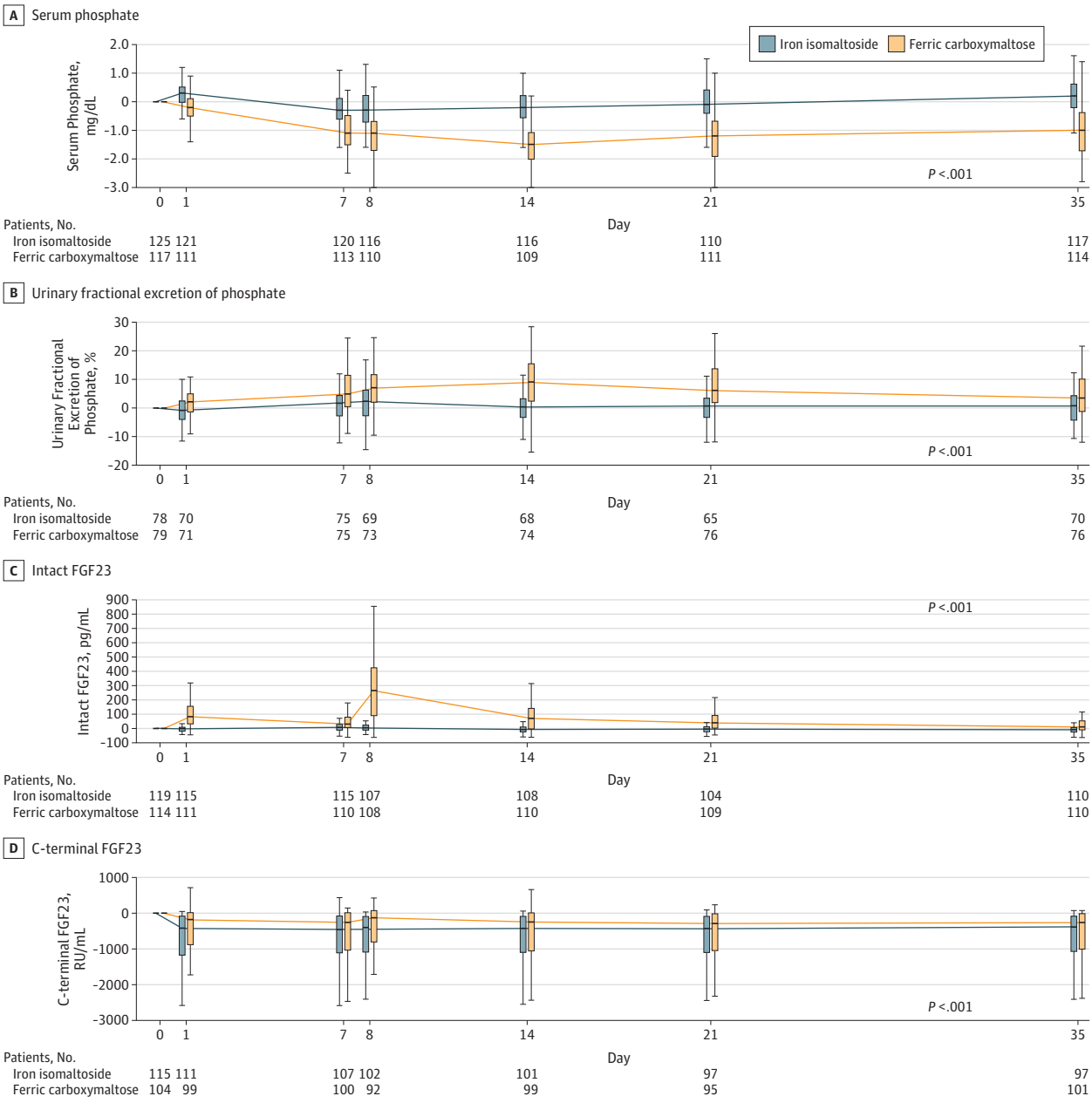
Overall, site investigators reported more frequent adverse drug reactions in the ferric carboxymaltose group vs the iron isomaltoside group (trial A: 27/60 [45.0%] vs 7/63 [11.1%]; trial B: 28/57 [49.1%] vs 14/62 [22.6%]; **Table 2**). In the ferric carboxymaltose group, hypophosphatemia and blood phosphorus decreased were reported as adverse drug reactions in 38.5% of patients (Table 2). After excluding these, rates of adverse drug reactions remained higher in the ferric carboxymaltose group vs the iron isomaltoside group (Table 2). Overall, serious or severe hypersensitivity reactions occurred in 1 patient (0.8%) in the iron isomaltoside group (swollen eyelid unilaterally) and in 2 patients (1.7%) in the ferric carboxymaltose group (dyspnea and swelling).

Discussion

In 2 randomized trials conducted in patients with iron-deficiency anemia who were intolerant of or unresponsive to oral iron, iron isomaltoside, compared with ferric carboxymaltose, resulted in lower incidence of hypophosphatemia over 35 days. These trials provide data about the incidence of an adverse effect that may have clinical consequences and mechanistic information about the role of fibroblast growth factor 23 in vitamin D metabolism in humans.

Detailed investigation of rare hereditary and acquired states of primary fibroblast growth factor 23 excess demonstrate that elevation of full-length, biologically active,

Figure 3. Changes From Baseline in Biomarkers of Mineral and Bone Homeostasis According to Iron Treatment: Pooled Data for Trial A and Trial B

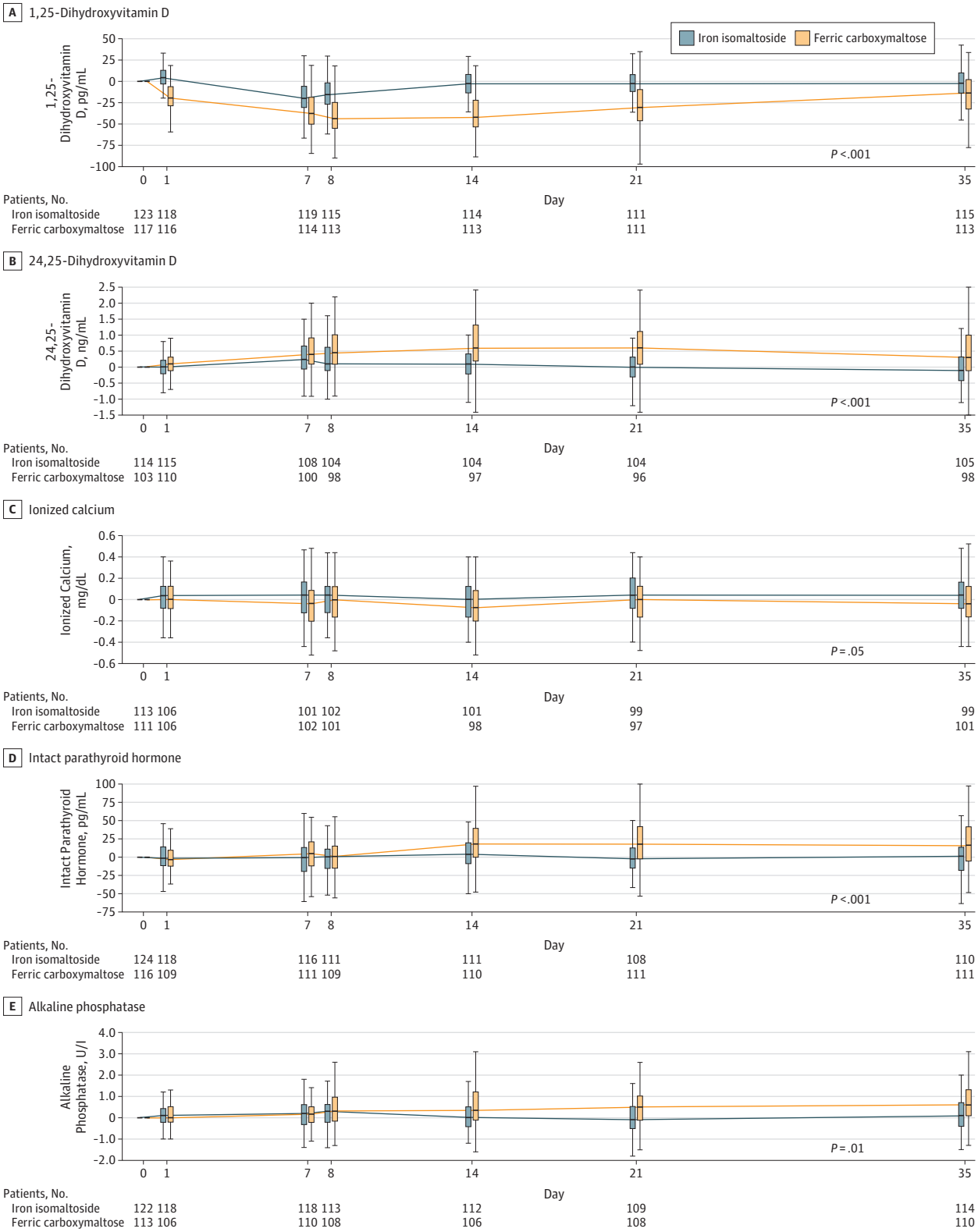


Tukey box plots indicate the interquartile range (25th, 75th percentiles) as vertical boxes, medians as horizontal lines within the boxes, and observations within 1.5 times above and below the interquartile range as vertical whiskers. Outliers are not shown. *P* values correspond to the treatment group-by-time interaction terms from the mixed models for repeated measures analyses of change from baseline in biomarkers, as described in the Methods section. FCM indicates ferric carboxymaltose; FGF23, fibroblast growth factor 23; and IIM, iron isomaltoside 1000 (now called ferric derisomaltose).

intact fibroblast growth factor 23 causes hypophosphatemia by reducing proximal tubular reabsorption of filtered phosphate, and by suppressing circulating concentrations of 1,25-dihydroxyvitamin D, which is the active form of vitamin D.[23-25] Reduced 1,25-dihydroxyvitamin D limits compensatory increases in dietary phosphate absorption that would otherwise occur in response to hypophosphatemia and limits dietary calcium absorption, which can decrease serum calcium.[23,25] Secondary hyperparathyroidism in response to decreased serum calcium helps to maintain serum calcium within the normal range, but can further exacerbate hypophosphatemia by promoting renal phosphate losses via the known phosphaturic effects of elevated PTH.[23,26]

The findings of these 2 trials suggest that ferric carboxymaltose activated this entire pathophysiological cascade by acutely increasing intact fibroblast growth factor 23 within 1 day. This was followed by increased urinary phosphate

Figure 4. Changes From Baseline in Biomarkers of Mineral and Bone Homeostasis According to Iron Treatment: Pooled Data for Trial A and Trial B



See the Figure 3 legend for descriptions of the data markers and analysis. FCM indicates ferric carboxymaltose; FGF23, fibroblast growth factor 23; and IIM, iron isomaltoside 1000 (now called ferric derisomaltose).

Table 2. Adverse Drug Reactions Occurring at a Frequency of 5% or Greater in Either Treatment Group in the Safety Analysis Set

	No. (%)					
	Trial A		Trial B		Pooled	
Adverse Drug Reactions[a]	Iron Isomaltoside (n = 63)	Ferric Carboxymaltose (n = 60)	Iron Isomaltoside (n = 62)	Ferric Carboxymaltose (n = 57)	Iron Isomaltoside (n = 125)	Ferric Carboxymaltose (n = 117)
Any adverse drug reaction	7 (11.1)	27 (45.0)	14 (22.6)	28 (49.1)	21 (16.8)	55 (47.0)
Specific adverse drug reactions						
Hypophosphatemia	0	12 (20.0)	2 (3.2)	14 (24.6)	2 (1.6)	26 (22.2)
Blood						
Phosphorus decreased	0	12 (20.0)	0	7 (12.3)	0	19 (16.2)
Parathyroid hormone increased	0	1 (1.7)	4 (6.5)	5 (8.8)	4 (3.2)	6 (5.1)
Headache	1 (1.6)	1 (1.7)	3 (4.8)	4 (7.0)	4 (3.2)	5 (4.3)
Nausea	0	4 (6.7)	1 (1.6)	4 (7.0)	1 (0.8)	8 (6.8)
Serum ferritin increased	0	0	0	3 (5.3)	0	3 (2.6)

[a] The reporting of adverse drug reactions uses standard methodology (MedDRA terms). The listings for adverse drug reactions reflect adverse events that were judged by the local site investigator to be related or possibly related to the study drugs. For laboratory assessments, local site investigators saw the values and judged whether the decreased or increased levels necessitated reporting as an adverse drug reaction.

excretion and decreased 1,25-dihydroxyvitamin D and ionized calcium, which precipitated secondary hyperparathyroidism that likely maintained renal phosphate wasting and hypophosphatemia even after intact fibroblast growth factor 23 returned toward normal. Although the mechanism by which ferric carboxymaltose acutely elevates intact fibroblast growth factor 23 remains unknown, it has been proposed that the carbohydrate carrier of iron in ferric carboxymaltose somehow inhibits cleavage of full-length fibroblast growth factor 23 that is normally upregulated in parallel with increased *FGF23* gene transcription in iron deficiency.[9,11,27]

Animal studies have demonstrated that fibroblast growth factor 23 lowers 1,25-dihydroxyvitamin D concentrations by reducing its production via inhibition of *Cyp27b1* (1α-hydroxylase) and by accelerating its degradation via stimulation of *Cyp24a1* (24-hydroxylase).[28] However, physiological evidence of the importance of fibroblast growth factor 23-mediated stimulation of the vitamin D degradation pathway in humans has been limited. The finding that ferric carboxymaltose significantly increased 24,25-dihydroxyvitamin D levels, a marker of increased 24-hydroxylase activity, in association with increased intact fibroblast growth factor 23, supports fibroblast growth factor 23–mediated activation of 24-hydroxylase as an important contributor to reduced 1,25-dihydroxyvitamin D in states of fibroblast growth factor 23 excess. Previous human studies may have failed to isolate the effects of fibroblast growth factor 23 on 24-hydroxylase because of competing effects of 1,25-dihydroxyvitamin D on the enzyme. For example, in states of chronically elevated fibroblast growth factor 23 in which 1,25-dihydroxyvitamin D levels are suppressed, the known effects of low 1,25-dihydroxyvitamin D to reduce levels of 24,25-dihydroxyvitamin D[24] likely obscured the effects of fibroblast growth factor 23 excess to elevate 24,25-dihydroxyvitamin D. In contrast, the acute effects of ferric carboxymaltose enabled confirmation that abrupt elevation of fibroblast growth factor 23 significantly activates 24-hydroxylase activity.

Although there are numerous case reports of skeletal complications of ferric carboxymaltose,[13,29-32] to our knowledge, no previous controlled studies investigated the effects of intravenous iron on biomarkers of bone turnover. Thus, an important finding of these trials is that ferric carboxymaltose induced increases in intact fibroblast growth factor 23 and its downstream metabolic consequences may have significant effects on bone, as evidenced by increased total and bone-specific alkaline phosphatase and decreases in N-terminal propeptide of type 1 collagen, and carboxy-terminal collagen crosslinks. The change in alkaline phosphatase, which is consistent with the pattern observed in patients with osteomalacia,[33,34] provides new evidence that even a single course of ferric carboxymaltose may adversely affect the skeleton and may help explain why repeated dosing of ferric carboxymaltose has been associated with osteomalacia and fractures.[13,29-32]

Limitations

These trials have several limitations. First, the preponderance of patients with gynecological causes of iron-deficiency anemia, who tend to have higher rates of hypophosphatemia,[10] likely explains the higher than anticipated incidence of hypophosphatemia following ferric carboxymaltose treatment; this may limit generalizability to other causes of iron-deficiency anemia.

Second, the dosing for ferric carboxymaltose and iron isomaltoside differed, which could have affected the results. However, a recent observational study that was conducted in Europe, where the dosing of both ferric carboxymaltose and iron isomaltoside were identical, demonstrated similarly higher rates of hypophosphatemia following ferric carboxymaltose vs iron isomaltoside,[35] suggesting that the dosing is not the main driver of the current results.

Third, the end of follow-up at day 35 precluded a complete assessment of the duration until serum phosphate, 1,25-dihydroxyvitamin D, PTH, and alkaline phosphatase levels normalized after a single course of ferric carboxymaltose.

Fourth, the trials did not measure clinical outcomes.

Fifth, while the second dose within a single course of ferric carboxymaltose induced larger magnitude effects on intact fibroblast growth factor 23 and mineral metabolism than the first, the trials did not study whether the effects are further magnified by repeated courses of ferric carboxymaltose. Testing for such dose-stacking effects—whereby a second course of ferric carboxymaltose given during or shortly after an episode of hypophosphatemia from a prior course precipitates more severe and more protracted hypophosphatemia—is needed to further investigate the pathogenesis of ferric carboxymaltose–associated osteomalacia. However, this may be impossible in a controlled study because it would be ethically unacceptable to administer another course of ferric carboxymaltose to a patient who remains hypophosphatemic from a previous course.

Conclusions

In 2 randomized trials of patients with iron-deficiency anemia who were intolerant of or unresponsive to oral iron, iron isomaltoside, compared with ferric carboxymaltose, resulted in lower incidence of hypophosphatemia over 35 days. However, further research is needed to determine the clinical importance of this difference.

ARTICLE INFORMATION

Accepted for Publication: December 21, 2019.

Author Affiliations: Duke Clinical Research Institute, Division of Nephrology, Department of Medicine, Duke University School of Medicine, Durham, North Carolina (Wolf); Division of Endocrinology, Department of Medicine, University of North Carolina at Chapel Hill (Rubin); Harvard Medical School, Boston, Massachusetts (Achebe); Division of Endocrinology, Department of Medicine, Indiana University School of Medicine, Indianapolis (Econs, Peacock, Imel); Department of Clinical and Non-clinical Research, Pharmacosmos A/S, Holbæk, Denmark (Thomsen); Department of Pediatrics (Endocrinology), Yale University School of Medicine, New Haven, Connecticut (Carpenter); Division of Endocrinology, Metabolism and Nutrition, Department of Medicine, Duke University School of Medicine, Durham, North Carolina (Weber); Rhein-Maas Klinikum Würselen, Würselen, Germany (Brandenburg); Department of Medicine I, Medical University of Innsbruck, Innsbruck, Austria (Zoller).

Author Contributions: Drs Wolf and Zoller had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Wolf, Imel, Thomsen, Carpenter, Zoller.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Wolf, Rubin, Thomsen, Carpenter, Weber, Brandenburg, Zoller.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Wolf, Rubin, Brandenburg, Zoller.
Obtained funding: Thomsen.
Administrative, technical, or material support: Thomsen, Weber.
Supervision: Wolf, Rubin, Zoller.

Conflict of Interest Disclosures: Dr Wolf reported receiving personal fees from Pharmacosmos A/S during the conduct of the study and personal fees from AMAG Pharmaceuticals, Amgen, Akebia, Ardelyx, Keryx, and Luitpold Inc outside the submitted work. Dr Rubin reported receiving personal fees from Pharmacosmos A/S during the conduct of the study. Dr Achebe reported serving as a consultant to Pharmacosmos A/S and AMAG Pharmaceuticals during the conduct of the study and serving as a scientific advisory board member for Global Blood Therapeutics and Fulcrum Therapeutics and receiving personal fees from Bluebird Bio outside the submitted work. Dr Econs reported receiving personal fees from Pharmacosmos A/S during the conduct of the study. Dr Peacock reported receiving personal fees from Pharmacosmos A/S and Ultragenyx during the conduct of the study. Dr Imel reported receiving personal fees from Pharmacosmos A/S during the conduct of the study for consulting and personal fees from American Regent Inc outside the submitted work for consulting. Dr Thomsen reported being an employee of Pharmacosmos A/S and being a coinventor on pending patents related to iron isomatoside. Dr Carpenter reported receiving personal fees from Pharmacosmos A/S during the conduct of the study. Dr Weber reported receiving personal fees from Pharmacosmos A/S during the conduct of the study and grants and personal fees from Ultragenyx outside the submitted work. Dr Brandenburg reported receiving grants and personal fees from Pharmacosmos A/S and Vifor Pharma outside the submitted work. Dr Zoller reported receiving grants, personal fees, and nonfinancial support from Pharmacosmos A/S and Vifor Pharma during the conduct of the study and grants, personal fees, and nonfinancial support from Abbvie and Gilead; personal fees from Merck; personal fees and nonfinancial support from Bayer; grants from Merck Sharp & Dohme; and honoraria for lecturing from Bristol-Myers Squibb, Merz, Medice, Novartis, Pharmacosmos A/S, and Vifor Pharma outside the submitted work.

Funding/Support: Pharmacosmos A/S, Holbaek, Denmark, provided study drug, research funding to the participating investigators/institutions, and financial support that allowed analysis and interpretation of the data and the preparation of the manuscript.

Role of the Funder/Sponsor: Pharmacosmos A/S funded the study and was the Good Clinical Practice sponsor. In consultation with the steering committee, the sponsor participated in the design of both trials. The sponsor commissioned contract research organizations and was responsible for and coordinated protocol writing, preparation of the statistical analysis plan, data collection, writing of the clinical study report, project management, and data analysis. The sponsor and the steering committee interpreted the data; the sponsor reviewed and commented on the manuscript that was written by the academic authors. Journal selection was made by the academic author group and agreed on by the sponsor. The sponsor did not have the right to veto submission in general or to any particular journal.

Data Sharing Statement: See Supplement 5.

Additional Contributions: We thank all the investigators, trial personnel, and participating patients for their contributions to the trial. Data management and statistical analyses were provided by Biostata ApS, Birkeroed, Denmark. Medical writing support was provided by Jenny Muiry, PhD, assisted by her colleagues at Cambridge Medical Communication Ltd, Cambridge, United Kingdom; she received compensation for her contribution.

REFERENCES

1. Camaschella C. Iron-deficiency anemia. *N Engl J Med*. 2015;372(19):1832-1843. doi:10.1056/NEJMra1401038

2. Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. *Lancet*. 2016;387(10021):907-916. doi:10.1016/S0140-6736(15)60865-0

3. Girelli D, Ugolini S, Busti F, Marchi G, Castagna A. Modern iron replacement therapy: clinical and pathophysiological insights. *Int J Hematol*. 2018;107(1):16-30. doi:10.1007/s12185-017-2373-3

4. Bhandari S, Pereira DIA, Chappell HF, Drakesmith H. Intravenous irons: from basic science to clinical practice. *Pharmaceuticals (Basel)*. 2018;11(3):82. doi:10.3390/ph11030082

5. Derman R, Roman E, Modiano MR, Achebe MM, Thomsen LL, Auerbach M. A randomized trial of iron isomaltoside versus iron sucrose in patients with iron deficiency anemia. *Am J Hematol*. 2017;92(3):286-291. doi:10.1002/ajh.24633

6. Holm C, Thomsen LL, Norgaard A, Langhoff-Roos J. Single-dose intravenous iron infusion or oral iron for treatment of fatigue after postpartum haemorrhage: a randomized controlled trial. *Vox Sang*. 2017;112(3):219-228. doi:10.1111/vox.12477

7. Onken JE, Bregman DB, Harrington RA, et al. A multicenter, randomized, active-controlled study to investigate the efficacy and safety of intravenous ferric carboxymaltose in patients with iron deficiency anemia. *Transfusion*. 2014;54(2):306-315.

8. Onken JE, Bregman DB, Harrington RA, et al. Ferric carboxymaltose in patients with iron-deficiency anemia and impaired renal function: the REPAIR-IDA trial. *Nephrol Dial Transplant*. 2014;29(4):833-842. doi:10.1093/ndt/gft251

9. Wolf M, Koch TA, Bregman DB. Effects of iron deficiency anemia and its treatment on fibroblast growth factor 23 and phosphate homeostasis in women. *J Bone Miner Res*. 2013;28(8):1793-1803. doi:10.1002/jbmr.1923

10. Wolf M, Chertow GM, Macdougall IC, Kaper R, Krop J, Strauss W. Randomized trial of intravenous iron-induced hypophosphatemia. *JCI Insight*. 2018; 3(23):124486. doi:10.1172/jci.insight.124486

11. Edmonston D, Wolf M. FGF23 at the crossroads of phosphate, iron economy and erythropoiesis. *Nat Rev Nephrol*. 2020;16(1):7-19. doi:10.1038/s41581-019-0189-5

12. Subramanian R, Khardori R. Severe hypophosphatemia: pathophysiologic implications, clinical presentations, and treatment. *Medicine (Baltimore)*. 2000;79(1):1-8. doi:10.1097/00005792-200001000-00001

13. Zoller H, Schaefer B, Glodny B. Iron-induced hypophosphatemia: an emerging complication. *Curr Opin Nephrol Hypertens*. 2017;26(4):266-275. doi:10.1097/MNH.0000000000000329

14. Auerbach M, Lykke LL. A single infusion of iron isomaltoside 1000 allows a more rapid hemoglobin increment than multiple doses of iron sucrose with a similar safety profile in patients with iron deficiency anemia. *Blood*. 2018;132(suppl 1):2334. doi:10.1182/blood-2018-99-110199

15. Emrich IE, Lizzi F, Seiler-Mußler S, et al. Hypophosphatemia after high dosage iron substitution with ferric carboxymaltose (FCM) and iron isomaltoside (IM): the randomised controlled Home Afers 1 trial. *Blood*. 2018;132(suppl 1):3627. doi:10.1182/blood-2018-99-114386

16. US Food and Drug Administration. Highlights of prescribing information: Injectafer (ferric carboxymaltose injection). Vifor (International) Inc, Switzerland. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203565s005lbl.pdf. Revised January 2018. Accessed October 22, 2019.

17. Birgegård G, Henry D, Glaspy J, Chopra R, Thomsen LL, Auerbach M. A randomized noninferiority trial of intravenous iron isomaltoside versus oral iron sulfate in patients with nonmyeloid malignancies and anemia receiving chemotherapy: the PROFOUND trial. *Pharmacotherapy*. 2016;36 (4):402-414. doi:10.1002/phar.1729

18. Dahlerup JF, Jacobsen BA, van der Woude J, Bark LÅ, Thomsen LL, Lindgren S. High-dose fast infusion of parenteral iron isomaltoside is efficacious in inflammatory bowel disease patients with iron-deficiency anaemia without profound changes in phosphate or fibroblast growth factor 23. *Scand J Gastroenterol*. 2016;51(11):1332-1338. doi:10.1080/00365521.2016.1196496

19. Reinisch W, Staun M, Tandon RK, et al. A randomized, open-label, non-inferiority study of intravenous iron isomaltoside 1,000 (Monofer) compared with oral iron for treatment of anemia in IBD (PROCEED). *Am J Gastroenterol*. 2013;108 (12):1877-1888. doi:10.1038/ajg.2013.335

20. Van Wyck DB, Mangione A, Morrison J, Hadley PE, Jehle JA, Goodnough LT. Large-dose intravenous ferric carboxymaltose injection for iron deficiency anemia in heavy uterine bleeding: a randomized, controlled trial. *Transfusion*. 2009; 49(12):2719-2728. doi:10.1111/j.1537-2995.2009.02327.x

21. Favrat B, Balck K, Breymann C, et al. Evaluation of a single dose of ferric carboxymaltose in fatigued, iron-deficient women: PREFER a randomized, placebo-controlled study. *PLoS One*. 2014;9(4): e94217. doi:10.1371/journal.pone.0094217

22. Yan X, Su XG. Stratified Wilson and Newcombe confidence intervals for multiple binomial proportions. *Stat Biopharm Res*. 2010;2(3):329-335. doi:10.1198/sbr.2009.0049

23. Quarles LD. Endocrine functions of bone in mineral metabolism regulation. *J Clin Invest*. 2008; 118(12):3820-3828. doi:10.1172/JCI36479

24. Reichel H, Koeffler HP, Norman AW. The role of the vitamin D endocrine system in health and disease. *N Engl J Med*. 1989;320(15):980-991. doi: 10.1056/NEJM198904133201506

25. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357(3):266-281. doi:10.1056/NEJMra070553

26. Potts JT. Parathyroid hormone: past and present. *J Endocrinol*. 2005;187(3):311-325. doi:10.1677/joe.1.06057

27. Farrow EG, Yu X, Summers LJ, et al. Iron deficiency drives an autosomal dominant hypophosphatemic rickets (ADHR) phenotype in fibroblast growth factor-23 (Fgf23) knock-in mice. *Proc Natl Acad Sci U S A*. 2011;108(46):E1146-E1155. doi:10.1073/pnas.1110905108

28. Shimada T, Hasegawa H, Yamazaki Y, et al. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. *J Bone Miner Res*. 2004;19(3):429-435. doi:10.1359/JBMR.0301264

29. Klein K, Asaad S, Econs M, Rubin JE. Severe FGF23-based hypophosphataemic osteomalacia due to ferric carboxymaltose administration. *BMJ Case Rep*. 2018;2018:bcr-2017-222851. doi:10.1136/bcr-2017-222851

30. Schaefer B, Glodny B, Zoller H. Blood and bone loser. *Gastroenterology*. 2017;152(6):e5-e6. doi:10.1053/j.gastro.2016.09.050

31. Urbina T, Belkhir R, Rossi G, et al. Iron supplementation-induced phosphaturic osteomalacia: FGF23 is the culprit. *J Bone Miner Res*. 2018;33(3):540-542. doi:10.1002/jbmr.3369

32. Burckhardt P. Iron-induced osteomalacia. *Osteologie*. 2018;27(1):20-23.

33. Nagata Y, Imanishi Y, Ishii A, et al. Evaluation of bone markers in hypophosphatemic rickets/osteomalacia. *Endocrine*. 2011;40(2):315-317. doi:10.1007/s12020-011-9512-z

34. Peach H, Compston JE, Vedi S, Horton LWL. Value of plasma calcium, phosphate, and alkaline phosphatase measurements in the diagnosis of histological osteomalacia. *J Clin Pathol*. 1982;35(6): 625-630. doi:10.1136/jcp.35.6.625

35. Detlie TE, Lindstrøm JC, Jahnsen ME, et al. Incidence of hypophosphatemia in patients with inflammatory bowel disease treated with ferric carboxymaltose or iron isomaltoside. *Aliment Pharmacol Ther*. 2019;50(4):397-406. doi:10.1111/apt.15386

Supplementary Online Content

Wolf M, Rubin J, Achebe M, et al. Effects of iron isomaltoside vs ferric carboxymaltose on hypophosphatemia in iron-deficiency anemia: two randomized clinical trials [published February 4, 2020]. *JAMA*. doi:10.1001/jama.2019.22450

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Inclusion and Exclusion Criteria, and Main Revisions to the Trial Protocols

Inclusion and exclusion criteria, and changes implemented during the trial conduct
Inclusion criteria 1. Men or women >18 years with IDA caused by different etiologies,[a] such as abnormal uterine bleeding, gastrointestinal diseases, cancer, bariatric procedures (gastric bypass operations), and other conditions leading to significant blood loss. 2. Hb ≤11 g/dl. 3. Body weight >50 kg. 4. Serum ferritin ≤100 ng/ml. 5. Estimated glomerular filtration rate ≥65 ml/min/1.73 m^2. 6. Serum phosphate >2.5 mg/dl. 7. Documented history of intolerance or unresponsiveness to oral iron therapy[b] for at least one month[c] prior to trial enrollment. 8. Willingness to participate and signing the Informed Consent Form.
Exclusion criteria 1. Acute bleeding >500 ml within 72 hours. 2. Anaemia predominantly caused by factors other than IDA according to Investigator's judgment. 3. Hemochromatosis or other iron storage disorders. 4. Known hypersensitivity reaction to any component of IIM or FCM. 5. Previous serious hypersensitivity reactions to any IV iron compounds. 6. Treatment with IV iron within the last 30 days prior to screening. 7. Treatment with erythropoietin or erythropoietin-stimulation agents, red blood cell transfusion, radiotherapy, and/or chemotherapy within the last 30 days prior to screening. 8. Received an investigational drug within the last 30 days prior to screening. 9. Planned surgical procedure within the trial period. 10. Alanine aminotransferase and/or aspartate aminotransferase >3 times upper limit of normal (e.g., decompensated liver cirrhosis or active hepatitis). 11. Surgery under general anaesthesia within the last 30 days prior to screening. 12. Any non-viral infection within the last 30 days prior to screening. 13. Alcohol or drug abuse within the past 6 months. 14. Untreated hyperparathyroidism. 15. Kidney transplantation. 16. Estimated life expectancy of <6 months or, for cancer patients, an Eastern Cooperative Oncology Group (ECOG) performance status >1. 17. Conditions that interfere with the subject's ability to understand the requirements of the trial and/or presumable non-compliance. 18. Any other laboratory abnormality, medical condition, or psychiatric disorders which, in the opinion of the Investigator, will put the subject's disease management at risk or may result in the subject being unable to comply with the trial requirements. 19. Pregnant or nursing women. In order to avoid pregnancy, women of childbearing potential have to use adequate contraception (e.g., intrauterine devices, hormonal contraceptives, or double barrier method) during the entire trial period and 7 days after the last dosing.
Main revisions made to the trial protocols
The original protocols were amended once during the trials. Besides minor editing and administrative changes, the following amendments were made to the original protocol: • Text was updated to show that alkaline phosphatase was measured in serum and not in plasma. • The pyridinoline test – an exploratory end point with limited value – was omitted. • Exclusion criteria changes: Surgery under anesthesia was changed to surgery under general anesthesia; measurement of vitamin D prior to IV iron treatment was deleted as this is not standard; exclusion of oncology patients was a mistake and therefore this exclusion criterion was replaced with an inclusion criterion of life expectancy of at least 6 months; and psychological illness or seizures were omitted since neither were contraindicated or warned of in the prescribing information.

Main revisions made to the trial protocols (continued)
• "Documented history" was defined with the subject's own description of their illness deemed adequate to be entered in the medical file as source. Thus, no medical files from the referring physician or other were considered necessary. • Prohibited medications and non-drug therapies – erythropoietin or erythropoietin-stimulation agents, radiotherapy, and chemotherapy – were clarified as prohibited by alignment with exclusion criteria and prohibited medications. • Functional team positions within two internal teams – the TCT and GCP Quality Steering Committee – were expanded to reflect the updated team constitutions. • The description of trial summary data for posting in public registries was simplified to reflect updated requirements of the FDA "Final Rule".

[a] The etiology for IDA was documented in the medical history and verified in the source documents; if the etiology was unknown, this was also documented.

[b] Intolerance and non-response to oral iron treatment, along with the accompanying signs and symptoms, were documented in the medical history and verified in the source documents.

[c] Intolerance or unresponsiveness to ≥1 month of prescribed oral iron therapy according to the Investigator's judgment within the last 9 months was documented; these patients would not be candidates for oral iron again.

GCP, Good Clinical Practice; Hb, hemoglobin; FCM, ferric carboxymaltose; IDA, iron deficiency anemia; IIM iron isomaltoside 1000/ferric derisomaltose; IV, intravenous; TCT, Trial Core Team.

eTable 2. Listing of All Secondary Safety and Efficacy End Points

Secondary end point	Reported in manuscript?
Safety end points[a]	
Proportion of patients with hypophosphatemia at day 35	Yes
Absolute change in serum phosphate from baseline to days 1, 7, 8, 14, 21, and 35	Yes
Relative change in serum phosphate from baseline to days 1, 7, 8, 14, 21, and 35	No
Change in fractional urinary phosphate excretion from baseline to days 1, 7, 8, 14, 21, and 35	Yes
Change in intact fibroblast growth factor 23 from baseline to days 1, 7, 8, 14, 21, and 35	Yes
Change in C-terminal fibroblast growth factor 23 from baseline to days 1, 7, 8, 14, 21, and 35	Yes
Change in 1,25-Dihydroxyvitamin D from baseline to days 1, 7, 8, 14, 21, and 35	Yes
Change in 24,25-Dihydroxyvitamin D from baseline to days 1, 7, 8, 14, 21, and 35	Yes
Change in 25-Hydroxyvitamin D from baseline to days 1, 7, 8, 14, 21, and 35	Yes
Change in ionized calcium from baseline to days 1, 7, 8, 14, 21, and 35	Yes
Change in intact parathyroid hormone from baseline to days 1, 7, 8, 14, 21, and 35	Yes
Incidence of serum phosphate <1.0 mg/dl at any time from baseline to day 35	Yes[b]
Time with hypophosphatemia (serum phosphate <2.0 mg/dl) from baseline to day 35	No
Type and incidence of adverse events	Yes
Serious or severe hypersensitivity reactions (i.e., treatment-emergent)	Yes
Efficacy end points	
Change in hemoglobin per gram of iron from baseline to days 1, 7, 8, 14, 21, and 35	Yes
Change in ferritin from baseline to days 1, 7, 8, 14, 21, and 35	Yes
Change in transferrin saturation from baseline to days 1, 7, 8, 14, 21, and 35	Yes

[a] In addition, physical examinations and measurements of vital signs, height, weight, electro-cardiogram, and safety laboratory parameters were measured as part of standard safety assessments.

[b] The pre-specified secondary endpoint for severe hypophosphatemia was <1.0 mg/dl, whereas ≤1.0 mg/dl is reported in the manuscript. This modification of the definition of severe hypophosphatemia was enacted to account for rounding of values measured in mmol/l to two decimal places, into mg/dl reported to one decimal place, which caused values of 0.99 mg/dl (0.32 mmol/l) to be rounded to equal to rather than less than 1.0 mg/dl.

eTable 3. Biochemical Assays

Biochemical/ bone marker	Assay	Manufacturer	Precision (%CV)	
			Intra-assay	Inter-assay
Hemoglobin	Flow cytometry	Siemens ADVIA 2120i Hematology System	0.9–1.1	0.9–1.8
Serum phosphate	Photometric analysis	Roche Diagnostics	0.5–0.9	1.2–1.4
Urine phosphorus	Colorimetric	Roche Cobas 8000 Modular Analyzer	0.5–0.8	1.3–1.4
Ferritin	Chemiluminescence immunoassay	Beckman Coulter Inc.	2.6–3.9	4.1–6.3
Transferrin	Chemiluminescence immunoassay	Siemens BN II Nephelometer	2.7	2.3
Serum creatinine	Automated clinical chemistry	Roche Cobas 8000 Modular Analyzer	0.9–2.5	1.7–3.7
Urine creatinine	Colorimetric	Roche Cobas 8000 Modular Analyzer	1.1–2.1	1.7–2.2
Intact FGF23	ELISA	Immutopics, Inc.	2.0–4.1	3.5–9.1
C-terminal FGF23	ELISA	Immutopics, Inc.	1.4–2.4	2.4–4.7
25-Hydroxyvitamin D	LC-MS/MS	SCIEX	D2: 2.5–3.1 D3: 1.5–4.0	D2: 2.9–5.4 D3: 2.8–4.4
1,25-Dihydroxyvitamin D	Chemiluminescence immunoassay	DiaSorin	3.5–7.8	3.6–6.6
24,25-Dihydroxyvitamin D	LC-MS/MS	Danaher-SCIEX API5000	D2: 2.3–5.9 D3: 3.1–7.8	D2: 3.3–6.2 D3: 3.0–6.5
Ionized calcium	Ion-selective electrode	Instrumentation Laboratory	Not specified	Not specified
Intact parathyroid hormone	Chemiluminescence immunoassay	Siemens Healthcare Diagnostics	3.4–5.2	1.5–5.8
Alkaline phosphatase	Photometric analysis	Roche Diagnostics	0.4–0.5	0.67
Bone-specific alkaline phosphatase	Chemiluminescence immunoassay	Beckman Coulter Inc.	1.5–2.6	3.6–6.4
N-terminal propeptide of Type I collagen	Electrochemiluminescence immunoassay	Roche Diagnostics	1.6–2.1	4.2–4.4
Carboxy-terminal collagen crosslinks	Elecsys β-CrossLaps serum assay	Roche Diagnostics	1.3–2.3	4.6–6.5

Urinary fractional excretion of phosphate was calculated as: [urinary phosphate * serum creatinine] / [serum phosphate * urinary creatinine] * 100. Transferrin saturation was calculated as: [total serum iron (μmol/l) * 5.586] / [transferrin (g/l) *100] * 70.9.

CV, coefficient of variation; ELISA, enzyme-linked immunosorbent assay; FGF23, fibroblast growth factor; LC-MS/MS, liquid chromatography and tandem mass spectrometry.

eTable 4. Prevalence of Hypophosphatemia at Each Time Point – Trial A, Trial B and Pooled Data for Trials A and B

	Day						
	0 **n/N (%)**	**1** **n/N (%)**	**7** **n/N (%)**	**8** **n/N (%)**	**14** **n/N (%)**	**21** **n/N (%)**	**35** **n/N (%)**
Trial A							
IIM	0/63 (0.0)	0/59 (0.0)	2/60 (3.3)	3/57 (5.3)	1/58 (1.7)	1/54 (1.9)	1/59 (1.7)
FCM	0/60 (0.0)	1/56 (1.8)	24/58 (41.4)	24/57 (42.1)	38/56 (67.9)	28/56 (50.0)	24/58 (41.4)
Rate difference (95% CI)	–	–1.8 (–5.3, 1.7)[a]	–37.9 (–50.9, –22.9)	–36.2 (–49.6, –20.9)	–65.9 (–76.8, –48.9)	–47.2 (–60.1, –30.0)	–39.2 (–52.2, –23.3)
P value	–	*P* = .30	*P* < .001	*P* < .001	*P* < .001	*P* < .001	*P* < .001
Rate difference, overall incidence (95% CI)	–67.0 (–77.4, –51.5)						
P value	*P* < .001						
Site-adjusted rate difference, overall incidence (95% CI)[b]	–67.5 (–78.5, –49.8)						
P value	*P* < .001						
Trial B							
IIM	0/62 (0.0)	0/61 (0.0)	2/60 (3.3)	3/59 (5.1)	3/58 (5.2)	1/56 (1.8)	0/58 (0.0)
FCM	0/57 (0.0)	0/53 (0.0)	14/55 (25.5)	22/53 (41.5)	33/53 (62.3)	28/55 (50.9)	25/56 (44.6)
Rate difference (95% CI)	–	–	–22.0 (–35.1, –7.5)	–38.4 (–52.2, –22.5)	–57.1 (–69.5, –40.3)	–48.6 (–61.4, –31.6)	–44.6 (–57.7, –31.6)[a]
P value	–	–	*P* < .001	*P* < .001	*P* < .001	*P* < .001	*P* < .001
Rate difference, overall incidence (95% CI)	–65.8 (–76.6, –49.8)						
P value	*P* < .001						
Site-adjusted rate difference, overall incidence (95% CI)[b]	–69.2 (–79.8, –51.3)						
P value	*P* < .001						

	Day						
	0 **n/N (%)**	**1** **n/N (%)**	**7** **n/N (%)**	**8** **n/N (%)**	**14** **n/N (%)**	**21** **n/N (%)**	**35** **n/N (%)**
Pooled data for Trial A and Trial B							
IIM	0/125 (0.0)	0/120 (0.0)	4/120 (3.3)	6/116 (5.2)	4/116 (3.4)	2/110 (1.8)	1/117 (0.9)
FCM	0/117 (0.0)	1/109 (0.9)	38/113 (33.6)	46/110 (41.8)	71/109 (65.1)	56/111 (50.5)	49/114 (43.0)
Rate difference (95% CI)	–	–0.9 (–2.7, 0.9)[a]	–30.1 (–39.5, –20.5)	–37.3 (–47.1, –26.8)	–61.5 (–70.1, –50.8)	–48.1 (–57.4, –37.4)	–41.7 (–50.9, –31.1)
P value	–	*P* = .29	*P* < .001	*P* < .001	*P* < .001	*P* < .001	*P* < .001
Rate difference, overall incidence (95% CI)	–66.4 (–74.4, –55.8)						
P value	*P* < .001						
Site-adjusted rate difference, overall incidence (95% CI)[b]	–68.3 (–76.5, –56.5)						
P value	*P* < .001						

Data are presented for the safety analysis set. *P* values are for between-group comparisons. Rate differences with 95% Newcombe CI adjusted for stratum (and trial, in the pooled analyses) using the Cochran-Mantel-Haenszel method, unless otherwise stated. [a] Rate difference with 95% Newcombe CI adjusted for stratum (and trial, in the pooled analyses) using the Cochran-Mantel-Haenszel method could not be estimated due to lack of events. Unadjusted treatment difference and 95% CI presented. [b] Rate difference with 95% Newcombe CI adjusted for site using the Cochran-Mantel-Haenszel method (*post-hoc* analysis).

CI, confidence interval; FCM, ferric carboxymaltose; FGF, fibroblast growth factor; IIM, iron isomaltoside 1000/ferric derisomaltose.

eTable 5. Secondary and Additional Safety End Points – Trial A, Trial B, and Pooled Data for Trials A and B

End point		Day 0 Mean (SD) n	1 Mean (SD) n	7 Mean (SD) n	8 Mean (SD) n	14 Mean (SD) n	21 Mean (SD) n	35 Mean (SD) n
Trial A								
Serum phosphate (mg/dl)	IIM	3.3 (0.6) (n=63)	3.6 (0.5) (n=59)	3.2 (0.6) (n=60)	3.2 (0.6) (n=57)	3.2 (0.6) (n=58)	3.4 (0.6) (n=54)	3.5 (0.6) (n=59)
	FCM	3.3 (0.5) (n=60)	3.1 (0.5) (n=56)	2.2 (0.5) (n=58)	2.2 (0.6) (n=57)	1.9 (0.8) (n=56)	2.3 (1.0) (n=56)	2.4 (0.9) (n=58)
	P	–	*P* < .001	*P* < .001	*P* < .001	*P* < .001	*P* < .001	*P* < .001
Urinary fractional excretion of phosphate (%)	IIM	11.1 (6.7) (n=40)	10.3 (6.4) (n=41)	11.8 (5.7) (n=43)	12.1 (6.7) (n=40)	11.1 (5.8) (n=44)	11.6 (6.5) (n=42)	10.3 (4.7) (n=49)
	FCM	10.3 (4.7) (n=42)	12.8 (5.0) (n=40)	18.8 (8.2) (n=42)	19.4 (9.4) (n=42)	21.8 (11.3) (n=46)	18.7 (10.2) (n=47)	15.2 (9.2) (n=48)
	P	–	*P* < .001	*P* < .001	*P* < .001	*P* < .001	*P* < .001	*P* = .001
Intact FGF23 (pg/ml)	IIM	59.0 (39.8) (n=59)	61.1 (58.2) (n=58)	69.0 (44.4) (n=60)	64.2 (32.4) (n=54)	51.2 (40.4) (n=57)	56.0 (49.1) (n=54)	48.2 (26.1) (n=58)
	FCM	46.2 (20.5) (n=57)	151.2 (90.1) (n=55)	118.1 (79.7) (n=56)	343.6 (257.7) (n=56)	151.0 (111.4) (n=56)	111.9 (94.2) (n=55)	79.0 (62.3) (n=57)
	P	–	*P* < .001	*P* < .001	*P* < .001	*P* < .001	*P* < .001	*P* < .001
C-terminal FGF23 (RU/ml)	IIM	847.1 (811.6) (n=60)	137.7 (72.3) (n=57)	119.1 (41.1) (n=55)	129.6 (93.3) (n=55)	107.2 (39.0) (n=57)	105.0 (47.3) (n=51)	109.2 (44.9) (n=53)
	FCM	631.2 (672.6) (n=55)	218.0 (122.1) (n=53)	161.6 (72.9) (n=55)	304.3 (172.4) (n=55)	193.6 (128.8) (n=55)	138.6 (64.7) (n=53)	122.2 (58.2) (n=57)
	P	–	*P* < .001	*P* < .001	*P* < .001	*P* < .001	*P* < .001	*P* = .14
1,25-Dihydroxyvitamin D (pg/ml)	IIM	58.9 (18.2) (n=62)	63.2 (23.9) (n=59)	39.2 (18.4) (n=60)	42.4 (19.0) (n=58)	55.2 (14.0) (n=58)	55.8 (15.5) (n=56)	55.2 (16.3) (n=59)
	FCM	63.9 (19.4) (n=60)	43.3 (17.2) (n=58)	25.1 (21.0) (n=58)	24.4 (25.3) (n=58)	24.9 (22.4) (n=57)	34.9 (28.4) (n=56)	46.0 (23.4) (n=58)
	P	–	*P* < .001	*P* < .001	*P* < .001	*P* < .001	*P* < .001	*P* = .004
24,25-Dihydroxyvitamin D (ng/ml)	IIM	2.1 (1.1) (n=61)	2.1 (0.9) (n=59)	2.4 (1.2) (n=60)	2.3 (1.2) (n=58)	2.2 (1.1) (n=58)	2.2 (1.3) (n=56)	2.2 (1.2) (n=59)
	FCM	2.4 (1.2) (n=56)	2.5 (1.3) (n=58)	3.2 (1.6) (n=58)	3.2 (1.6) (n=58)	3.5 (1.6) (n=56)	3.3 (1.5) (n=55)	3.1 (1.5) (n=58)
	P	–	*P* = .06	*P* = .002	*P* < .001	*P* < .001	*P* < .001	*P* = .001

End point		Day 0 Mean (SD) n	Day 1 Mean (SD) n	Day 7 Mean (SD) n	Day 8 Mean (SD) n	Day 14 Mean (SD) n	Day 21 Mean (SD) n	Day 35 Mean (SD) n
Trial A (continued)								
25-Hydroxyvitamin D (ng/ml)	IIM	23.2 (7.6) (n=62)	23.7 (7.4) (n=59)	24.5 (7.9) (n=60)	23.9 (7.8) (n=58)	24.2 (8.0) (n=58)	24.2 (8.2) (n=55)	23.4 (8.1) (n=59)
	FCM	25.9 (7.8) (n=60)	26.2 (8.0) (n=58)	25.3 (8.2) (n=57)	26.2 (8.3) (n=58)	25.1 (8.5) (n=57)	25.5 (7.6) (n=57)	26.0 (6.5) (n=56)
	P	–	*P* = .56	*P* = .01	*P* = .61	*P* = .04	*P* = .24	*P* = .83
Ionized calcium (mg/dl)	IIM	5.08 (0.21) (n=59)	5.12 (0.22) (n=56)	5.10 (0.19) (n=55)	5.11 (0.20) (n=54)	5.09 (0.22) (n=56)	5.13 (0.20) (n=54)	5.10 (0.24) (n=51)
	FCM	5.08 (0.21) (n=60)	5.08 (0.23) (n=56)	5.02 (0.17) (n=56)	5.05 (0.20) (n=56)	5.00 (0.20) (n=53)	5.03 (0.23) (n=50)	5.05 (0.24) (n=55)
	P	–	*P* = .27	*P* = .004	*P* = .05	*P* = .005	*P* = .006	*P* = .13
Intact parathyroid hormone (pg/ml)	IIM	55.1 (26.4) (n=62)	52.8 (25.6) (n=57)	50.8 (27.6) (n=58)	55.7 (32.4) (n=55)	59.5 (33.9) (n=55)	54.6 (29.4) (n=53)	55.5 (28.3) (n=54)
	FCM	51.6 (26.4) (n=59)	54.1 (23.5) (n=54)	58.5 (29.7) (n=57)	54.8 (28.7) (n=56)	68.3 (37.5) (n=57)	68.0 (34.7) (n=56)	72.7 (45.2) (n=57)
	P	–	*P* = .74	*P* = .04	*P* = .92	*P* = .06	*P* < .001	*P* = .003
Alkaline phosphatase (IU/l) (exploratory end point)	IIM	70.0 (26.9) (n=62)	70.3 (25.8) (n=59)	72.1 (22.4) (n=60)	72.7 (21.7) (n=57)	71.5 (22.0) (n=57)	71.3 (21.0) (n=56)	73.5 (25.4) (n=59)
	FCM	72.4 (27.5) (n=58)	72.1 (30.6) (n=54)	74.6 (28.2) (n=58)	78.8 (30.9) (n=58)	78.6 (32.0) (n=56)	81.9 (30.0) (n=56)	81.9 (31.0) (n=58)
	P	–	*P* = .96	*P* = .69	*P* = .14	*P* = .13	*P* = .005	*P* = .03
N-terminal propeptide of Type I collagen (ng/ml)	IIM	56.5 (26.3) (n=62)	55.0 (27.4) (n=59)	48.4 (21.5) (n=60)	48.7 (21.1) (n=58)	51.2 (25.6) (n=58)	53.4 (23.2) (n=56)	53.8 (25.7) (n=59)
	FCM	57.3 (28.9) (n=60)	54.8 (28.4) (n=58)	44.6 (23.0) (n=58)	45.2 (21.9) (n=57)	37.3 (17.9) (n=56)	38.4 (17.9) (n=54)	45.0 (19.1) (n=58)
	P	–	*P* = .92	*P* = .02	*P* = .03	*P* < .001	*P* < .001	*P* = .001
Carboxy-terminal collagen crosslinks (ng/ml)	IIM	0.33 (0.16) (n=61)	0.37 (0.19) (n=59)	0.31 (0.15) (n=59)	0.35 (0.18) (n=55)	0.34 (0.20) (n=57)	0.37 (0.21) (n=55)	0.37 (0.21) (n=57)
	FCM	0.29 (0.15) (n=58)	0.28 (0.15) (n=55)	0.25 (0.13) (n=57)	0.25 (0.12) (n=55)	0.24 (0.11) (n=56)	0.27 (0.13) (n=55)	0.30 (0.17) (n=58)
	P	–	*P* = .01	*P* = .02	*P* < .001	*P* < .001	*P* < .001	*P* = .10

End point		Day 0 Mean (SD) n	1 Mean (SD) n	7 Mean (SD) n	8 Mean (SD) n	14 Mean (SD) n	21 Mean (SD) n	35 Mean (SD) n
Trial B								
Serum phosphate (mg/dl)	IIM	3.4 (0.5) (n=62)	3.6 (0.5) (n=61)	3.0 (0.6) (n=60)	3.0 (0.6) (n=59)	3.1 (0.6) (n=58)	3.3 (0.5) (n=56)	3.5 (0.5) (n=58)
	FCM	3.3 (0.5) (n=57)	3.1 (0.4) (n=53)	2.5 (0.7) (n=55)	2.2 (0.7) (n=53)	1.8 (0.7) (n=53)	2.1 (0.9) (n=55)	2.3 (0.9) (n=56)
	P	–	*P* < .001	*P* < .001	*P* < .001	*P* < .001	*P* < .001	*P* < .001
Urinary fractional excretion of phosphate (%)	IIM	9.4 (4.9) (n=38)	10.2 (6.1) (n=38)	10.8 (5.8) (n=44)	12.4 (6.1) (n=43)	10.3 (4.9) (n=45)	10.0 (4.0) (n=46)	10.9 (5.7) (n=52)
	FCM	10.2 (4.5) (n=37)	11.4 (4.3) (n=36)	14.9 (6.5) (n=39)	15.7 (6.0) (n=37)	18.4 (10.0) (n=41)	16.9 (7.9) (n=44)	15.5 (8.4) (n=50)
	P	–	*P* = .21	*P* = .004	*P* = .001	*P* < .001	*P* < .001	*P* = .007
Intact FGF23 (pg/ml)	IIM	60.9 (50.3) (n=60)	55.6 (50.1) (n=61)	77.7 (62.9) (n=60)	69.4 (50.0) (n=59)	55.7 (45.9) (n=57)	52.8 (44.3) (n=56)	51.7 (46.6) (n=58)
	FCM	53.6 (35.3) (n=57)	147.8 (104.2) (n=54)	87.1 (73.1) (n=56)	311.6 (222.5) (n=54)	127.5 (104.5) (n=56)	107.9 (84.9) (n=56)	64.7 (49.4) (n=55)
	P	–	*P* < .001	*P* = .11	*P* < .001	*P* < .001	*P* < .001	*P* = .004
C-terminal FGF23 (RU/ml)	IIM	835.4 (802.2) (n=55)	136.5 (77.6) (n=61)	130.5 (126.7) (n=61)	108.4 (49.2) (n=57)	96.7 (45.2) (n=53)	96.7 (47.8) (n=55)	104.9 (63.4) (n=53)
	FCM	1060.9 (1799.4) (n=49)	239.0 (120.1) (n=52)	141.3 (85.4) (n=55)	319.3 (152.5) (n=48)	158.1 (88.8) (n=55)	143.9 (64.5) (n=53)	115.4 (85.7) (n=55)
	P	–	*P* = .12	*P* = .55	*P* < .001	*P* = .35	*P* = .20	*P* = .44
1,25-Dihydroxyvitamin D (pg/ml)	IIM	55.6 (16.4) (n=61)	61.0 (16.8) (n=60)	38.6 (17.9) (n=61)	41.6 (16.1) (n=59)	54.6 (17.6) (n=58)	55.3 (14.9) (n=57)	55.7 (15.1) (n=58)
	FCM	59.6 (19.6) (n=57)	42.6 (18.2) (n=56)	36.0 (30.6) (n=56)	25.0 (22.9) (n=55)	23.8 (21.7) (n=56)	35.9 (25.5) (n=55)	46.7 (22.9) (n=55)
	P	–	*P* < .001	*P* = .29	*P* < .001	*P* < .001	*P* < .001	*P* = .03
24,25-Dihydroxyvitamin D (ng/ml)	IIM	2.0 (1.6) (n=53)	2.0 (1.5) (n=54)	2.3 (1.7) (n=53)	2.1 (1.6) (n=50)	2.1 (1.6) (n=50)	2.0 (1.6) (n=52)	2.1 (1.6) (n=50)
	FCM	1.9 (1.1) (n=47)	2.0 (1.0) (n=46)	2.2 (1.1) (n=47)	2.3 (1.1) (n=45)	2.5 (1.2) (n=46)	2.4 (1.2) (n=46)	2.2 (0.9) (n=45)
	P	–	*P* = .51	*P* = .76	*P* = .32	*P* = .002	*P* < .001	*P* = .11

End point		Day 0 Mean (SD) n	Day 1 Mean (SD) n	Day 7 Mean (SD) n	Day 8 Mean (SD) n	Day 14 Mean (SD) n	Day 21 Mean (SD) n	Day 35 Mean (SD) n
Trial B (continued)								
25-Hydroxyvitamin D (ng/ml)	IIM	23.2 (11.0) (n=56)	22.6 (10.2) (n=54)	22.6 (10.3) (n=55)	22.3 (10.4) (n=51)	22.1 (10.1) (n=51)	22.2 (10.1) (n=51)	23.7 (9.7) (n=50)
	FCM	23.8 (10.0) (n=48)	23.9 (10.0) (n=47)	24.8 (10.3) (n=47)	25.3 (10.2) (n=45)	24.8 (10.4) (n=46)	24.4 (9.6) (n=45)	23.8 (8.1) (n=44)
	P	–	*P* = .69	*P* = .10	*P* = .02	*P* = .02	*P* = .10	*P* = .89
Ionized calcium (mg/dl)	IIM	5.11 (0.21) (n=54)	5.11 (0.20) (n=57)	5.13 (0.21) (n=55)	5.12 (0.21) (n=56)	5.05 (0.51) (n=52)	5.14 (0.19) (n=56)	5.13 (0.24) (n=56)
	FCM	5.07 (0.22) (n=51)	5.13 (0.22) (n=47)	5.07 (0.21) (n=51)	5.07 (0.22) (n=49)	5.01 (0.23) (n=48)	5.07 (0.23) (n=53)	5.05 (0.23) (n=50)
	P	–	*P* = .30	*P* = .16	*P* = .13	*P* = .94	*P* = .04	*P* = .24
Intact parathyroid hormone (pg/ml)	IIM	55.4 (26.5) (n=62)	55.7 (25.3) (n=60)	54.6 (24.4) (n=59)	53.9 (27.5) (n=57)	62.3 (32.2) (n=56)	56.4 (30.8) (n=56)	54.0 (29.0) (n=57)
	FCM	59.9 (33.9) (n=57)	53.3 (28.5) (n=54)	62.1 (34.7) (n=55)	58.2 (31.3) (n=54)	83.4 (40.5) (n=54)	83.4 (45.2) (n=56)	83.5 (45.5) (n=55)
	P	–	*P* = .22	*P* = .30	*P* = .92	*P* = .003	*P* < .001	*P* < .001
Alkaline phosphatase (IU/l) (exploratory end point)	IIM	71.8 (18.5) (n=60)	72.0 (17.8) (n=61)	72.1 (16.5) (n=60)	72.3 (16.6) (n=59)	69.6 (16.8) (n=58)	68.4 (17.4) (n=56)	70.8 (18.0) (n=58)
	FCM	76.9 (26.8) (n=55)	79.0 (27.7) (n=51)	78.8 (28.7) (n=55)	79.9 (29.3) (n=53)	81.7 (37.9) (n=53)	83.4 (50.5) (n=55)	83.8 (39.7) (n=56)
	P	–	*P* = .32	*P* = .22	*P* = .08	*P* = .05	*P* = .16	*P* = .04
N-terminal propeptide of Type I collagen (ng/ml)	IIM	58.4 (25.4) (n=60)	56.6 (23.3) (n=61)	49.8 (19.9) (n=60)	50.0 (20.8) (n=59)	50.1 (21.4) (n=57)	53.6 (22.0) (n=57)	55.6 (21.1) (n=58)
	FCM	65.6 (39.4) (n=57)	59.7 (30.3) (n=56)	53.8 (30.2) (n=56)	52.2 (29.0) (n=55)	48.3 (27.2) (n=53)	49.2 (33.2) (n=56)	53.2 (35.4) (n=56)
	P	–	*P* = .35	*P* = .83	*P* = .18	*P* < .001	*P* < .001	*P* = .01
Carboxy-terminal collagen crosslinks (ng/ml)	IIM	0.33 (0.15) (n=61)	0.37 (0.20) (n=61)	0.32 (0.18) (n=61)	0.33 (0.19) (n=59)	0.32 (0.16) (n=57)	0.35 (0.16) (n=56)	0.34 (0.17) (n=57)
	FCM	0.38 (0.22) (n=57)	0.34 (0.17) (n=56)	0.34 (0.21) (n=56)	0.28 (0.15) (n=54)	0.31 (0.17) (n=56)	0.34 (0.19) (n=56)	0.39 (0.21) (n=56)
	P	–	*P* = .01	*P* = .34	*P* < .001	*P* = .06	*P* = .15	*P* = .74

End point		Day 0 Mean (SD) n	Day 1 Mean (SD) n	Day 7 Mean (SD) n	Day 8 Mean (SD) n	Day 14 Mean (SD) n	Day 21 Mean (SD) n	Day 35 Mean (SD) n
Pooled data for Trial A and Trial B								
Serum phosphate (mg/dl)	IIM	3.4 (0.5) (n=125)	3.6 (0.5) (n=120)	3.1 (0.6) (n=120)	3.1 (0.6) (n=116)	3.2 (0.6) (n=116)	3.3 (0.6) (n=110)	3.5 (0.6) (n=117)
	FCM	3.3 (0.5) (n=117)	3.1 (0.5) (n=109)	2.3 (0.6) (n=113)	2.2 (0.6) (n=110)	1.9 (0.7) (n=109)	2.2 (1.0) (n=111)	2.4 (0.9) (n=114)
	P	–	*P* < .001	*P* < .001	*P* < .001	*P* < .001	*P* < .001	*P* < .001
Urinary fractional excretion of phosphate (%)	IIM	10.3 (5.9) (n=78)	10.2 (6.2) (n=79)	11.3 (5.7) (n=87)	12.3 (6.4) (n=83)	10.7 (5.4) (n=89)	10.7 (5.4) (n=88)	10.6 (5.2) (n=101)
	FCM	10.3 (4.6) (n=79)	12.2 (4.7) (n=76)	16.9 (7.7) (n=81)	17.7 (8.1) (n=79)	20.2 (10.8) (n=87)	17.8 (9.2) (n=91)	15.4 (8.8) (n=98)
	P	–	*P* < .001	*P* < .001	*P* < .001	*P* < .001	*P* < .001	*P* < .001
Intact FGF23 (pg/ml)	IIM	59.9 (45.2) (n=119)	58.3 (54.0) (n=119)	73.3 (54.4) (n=120)	66.9 (42.4) (n=113)	53.5 (43.1) (n=114)	54.4 (46.5) (n=110)	49.9 (37.7) (n=116)
	FCM	49.9 (29.0) (n=114)	149.5 (96.9) (n=109)	102.6 (77.7) (n=112)	327.9 (240.5) (n=110)	139.2 (108.2) (n=112)	109.9 (89.3) (n=111)	72.0 (56.5) (n=112)
	P	–	*P* < .001	*P* < .001	*P* < .001	*P* < .001	*P* < .001	*P* < .001
C-terminal FGF23 (RU/ml)	IIM	841.5 (803.6) (n=115)	137.0 (74.8) (n=118)	125.1 (95.9) (n=116)	118.8 (74.6) (n=112)	102.2 (42.2) (n=110)	100.7 (47.5) (n=106)	107.0 (54.7) (n=106)
	FCM	833.7 (1338.9) (n=104)	228.4 (121.0) (n=105)	151.5 (79.7) (n=110)	311.3 (162.8) (n=103)	175.8 (111.6) (n=110)	141.3 (64.4) (n=106)	118.8 (72.8) (n=112)
	P	–	*P* < .001	*P* = .14	*P* < .001	*P* < .001	*P* < .001	*P* = .40
1,25-Dihydroxyvitamin D (pg/ml)	IIM	57.3 (17.3) (n=123)	62.1 (20.6) (n=119)	38.9 (18.1) (n=121)	42.0 (17.6) (n=117)	54.9 (15.9) (n=116)	55.6 (15.1) (n=113)	55.5 (15.6) (n=117)
	FCM	61.8 (19.5) (n=117)	43.0 (17.6) (n=114)	30.5 (26.6) (n=114)	24.7 (24.1) (n=113)	24.3 (21.9) (n=113)	35.4 (26.9) (n=111)	46.4 (23.1) (n=113)
	P	–	*P* < .001	*P* < .001	*P* < .001	*P* < .001	*P* < .001	*P* < .001
24,25-Dihydroxyvitamin D (ng/ml)	IIM	2.0 (1.4) (n=114)	2.0 (1.3) (n=113)	2.3 (1.5) (n=113)	2.2 (1.4) (n=108)	2.2 (1.4) (n=108)	2.1 (1.4) (n=108)	2.1 (1.4) (n=109)
	FCM	2.2 (1.2) (n=103)	2.3 (1.2) (n=104)	2.7 (1.5) (n=105)	2.8 (1.5) (n=103)	3.0 (1.5) (n=102)	2.9 (1.4) (n=101)	2.7 (1.4) (n=103)
	P	–	*P* = .07	*P* = .04	*P* < .001	*P* < .001	*P* < .001	*P* < .001

End point		Day 0 Mean (SD) n	Day 1 Mean (SD) n	Day 7 Mean (SD) n	Day 8 Mean (SD) n	Day 14 Mean (SD) n	Day 21 Mean (SD) n	Day 35 Mean (SD) n
Pooled data for Trial A and Trial B (continued)								
25-Hydroxyvitamin D (ng/ml)	IIM	23.2 (9.4) (n=118)	23.2 (8.8) (n=113)	23.6 (9.1) (n=115)	23.2 (9.1) (n=109)	23.2 (9.0) (n=109)	23.3 (9.2) (n=106)	23.6 (8.8) (n=109)
	FCM	25.0 (8.9) (n=108)	25.2 (9.0) (n=105)	25.1 (9.1) (n=104)	25.8 (9.1) (n=103)	24.9 (9.3) (n=103)	25.0 (8.5) (n=102)	25.0 (7.3) (n=100)
	P	–	*P* = .46	*P* = .35	*P* = .30	*P* = .71	*P* > .99	*P* = .94
Ionized calcium (mg/dl)	IIM	5.09 (0.21) (n=113)	5.11 (0.21) (n=113)	5.11 (0.20) (n=110)	5.12 (0.21) (n=110)	5.07 (0.39) (n=108)	5.13 (0.20) (n=110)	5.12 (0.24) (n=107)
	FCM	5.08 (0.22) (n=111)	5.10 (0.22) (n=103)	5.04 (0.19) (n=107)	5.06 (0.21) (n=105)	5.00 (0.21) (n=101)	5.05 (0.23) (n=103)	5.05 (0.24) (n=105)
	P	–	*P* = .87	*P* = .003	*P* = .01	*P* = .21	*P* < .001	*P* = .06
Intact parathyroid hormone (pg/ml)	IIM	55.3 (26.3) (n=124)	54.3 (25.4) (n=117)	52.7 (26.0) (n=117)	54.8 (29.9) (n=112)	60.9 (32.9) (n=111)	55.5 (30.0) (n=109)	54.7 (28.5) (n=111)
	FCM	55.7 (30.5) (n=116)	53.7 (26.0) (n=108)	60.3 (32.1) (n=112)	56.4 (29.9) (n=110)	75.6 (39.5) (n=111)	75.7 (40.9) (n=112)	78.0 (45.5) (n=112)
	P	–	*P* = .44	*P* = .02	*P* = .93	*P* < .001	*P* < .001	*P* < .001
Alkaline phosphatase (IU/l) (exploratory end point)	IIM	70.9 (23.1) (n=122)	71.1 (22.0) (n=120)	72.1 (19.6) (n=120)	72.5 (19.2) (n=116)	70.5 (19.5) (n=115)	69.9 (19.3) (n=112)	72.1 (22.0) (n=117)
	FCM	74.6 (27.1) (n=113)	75.5 (29.3) (n=105)	76.6 (28.4) (n=113)	79.3 (30.0) (n=111)	80.1 (34.9) (n=109)	82.7 (41.2) (n=111)	82.8 (35.4) (n=114)
	P	–	*P* = .64	*P* = .29	*P* = .02	*P* = .01	*P* = .003	*P* = .002
N-terminal propeptide of Type I collagen (ng/ml)	IIM	57.4 (25.7) (n=122)	55.8 (25.3) (n=120)	49.1 (20.7) (n=120)	49.3 (20.9) (n=117)	50.6 (23.5) (n=115)	53.5 (22.5) (n=113)	54.7 (23.4) (n=117)
	FCM	61.4 (34.5) (n=117)	57.2 (29.3) (n=114)	49.1 (27.0) (n=114)	48.7 (25.8) (n=112)	42.6 (23.4) (n=109)	43.9 (27.2) (n=110)	49.0 (28.5) (n=114)
	P	–	*P* = .36	*P* = .07	*P* = .01	*P* < .001	*P* < .001	*P* < .001
Carboxy-terminal collagen crosslinks (ng/ml)	IIM	0.33 (0.16) (n=122)	0.37 (0.19) (n=120)	0.32 (0.16) (n=120)	0.34 (0.18) (n=114)	0.33 (0.18) (n=114)	0.36 (0.19) (n=111)	0.36 (0.19) (n=114)
	FCM	0.34 (0.20) (n=115)	0.31 (0.16) (n=111)	0.29 (0.18) (n=113)	0.26 (0.14) (n=109)	0.28 (0.14) (n=112)	0.31 (0.17) (n=111)	0.35 (0.20) (n=114)
	P	–	*P* < .001	*P* = .04	*P* < .001	*P* < .001	*P* < .001	*P* = .23

Data are presented for the safety analysis set. *P* values are for between-group comparisons from a mixed model for repeated measures analysis with treatment, day, treatment-by-day, trial (in the pooled analysis) and stratum as fixed effects and baseline value and baseline value-by-day as covariates.

CI, confidence interval; FCM, ferric carboxymaltose; FGF, fibroblast growth factor; IIM, iron isomaltoside 1000/ferric derisomaltose; SD, standard deviation.

eTable 6. Least Squares Mean Changes From Baseline in Biochemical and Bone Markers – Trial A, Trial B, and Pooled Data for Trials A and B

Trial A

Biochemical/bone marker	IIM	FCM	Difference between IIM and FCM (95% CI)	P Value
Serum phosphate (mg/dl)				
Day 1	0.24	–0.23	0.48 (0.31,0.65)	< .001
Day 7	–0.07	–1.13	1.06 (0.85,1.27)	< .001
Day 8	–0.09	–1.12	1.03 (0.81,1.25)	< .001
Day 14	–0.08	–1.42	1.35 (1.10,1.60)	< .001
Day 21	0.02	–1.02	1.03 (0.75,1.32)	< .001
Day 35	0.22	–0.91	1.13 (0.86,1.39)	< .001
Fractional urinary excretion of phosphate (%)				
Day 1	–1.6	2.3	–3.9 (–5.9,–1.9)	< .001
Day 7	0.9	7.9	–7.1 (–10.3,–3.8)	< .001
Day 8	1.5	8.9	–7.3 (–11.2,–3.5)	< .001
Day 14	0.7	11.2	–10.4 (–14.9,–6.0)	< .001
Day 21	0.7	8.7	–8.1 (–12.2,–3.9)	< .001
Day 35	–1.3	4.5	–5.8 (–9.2,–2.4)	.001
Intact FGF23 (pg/ml)				
Day 1	–2.1	103.6	–105.7 (–131.0,–80.5)	< .001
Day 7	8.6	69.4	–60.8 (–83.0,–38.6)	< .001
Day 8	13.4	306.6	–293.2 (–368.2,–218.3)	< .001
Day 14	–5.9	111.5	–117.5 (–151.6,–83.3)	< .001
Day 21	–0.2	71.0	–71.2 (–101.8,–40.6)	< .001
Day 35	–6.7	30.4	–37.2 (–54.9,–19.4)	< .001
C-terminal FGF23 (RU/ml)				
Day 1	–586.1	–487.0	–99.1 (–136.42,–61.76)	< .001
Day 7	–597.5	–548.2	–49.3 (–72.80,–25.90)	< .001
Day 8	–588.0	–396.7	–191.3 (–242.47,–140.09)	< .001
Day 14	–610.0	–509.3	–100.7 (–137.19,–64.20)	< .001
Day 21	–613.2	–564.8	–48.4 (–71.78,–24.96)	< .001
Day 35	–604.6	–589.7	–15.0 (–35.04, 5.06)	.14
Ionized calcium (mg/dl)				
Day 1	0.04	0.01	0.04 (–0.03, 0.10)	.27
Day 7	0.02	–0.06	0.09 (0.03,0.14)	.004
Day 8	0.04	–0.03	0.06 (0.00,0.13)	.05
Day 14	0.02	–0.09	0.10 (0.03,0.17)	.01
Day 21	0.06	–0.04	0.10 (0.03,0.17)	.01
Day 35	0.02	–0.03	0.06 (–0.02, 0.13)	.13
Parathyroid hormone (pg/ml)				
Day 1	–1.0	0.2	–1.1 (–8.0,5.7)	.74
Day 7	–3.4	6.4	–9.7 (–18.8,–0.6)	.04
Day 8	1.9	2.4	–0.5 (–10.6, 9.6)	.92
Day 14	5.1	16.3	–11.2 (–22.8, 0.5)	.06
Day 21	–1.9	16.3	–18.2 (–28.7,–7.7)	< .001
Day 35	1.8	21.6	–19.8 (–32.8,–6.8)	.003

Biochemical/bone marker	IIM	FCM	Difference between IIM and FCM (95% CI)	P Value
25-Hydroxyvitamin D (ng/ml)				
Day 1	0.1	0.3	–0.2 (–1.1,0.6)	.56
Day 7	0.8	–1.0	1.8 (0.4,3.1)	.01
Day 8	0.4	–0.0	0.4 (–1.2,2.0)	.61
Day 14	0.9	–1.2	2.1 (0.1,4.1)	.04
Day 21	0.5	–0.7	1.2 (–0.8,3.1)	.24
Day 35	–0.5	–0.3	–0.2 (–2.2,1.8)	.83
1,25-Dihydroxyvitamin D (pg/ml)				
Day 1	4.3	–20.0	24.3 (18.8,29.7)	< .001
Day 7	–21.4	–37.2	15.8 (8.8,22.7)	< .001
Day 8	–17.7	–37.8	20.1 (12.1,28.2)	< .001
Day 14	–5.4	–37.6	32.2 (25.5, 39.0)	< .001
Day 21	–4.9	–27.8	22.9 (14.8,31.0)	< .001
Day 35	–5.7	–16.3	10.6 (3.4,17.8)	.004
24,25-Dihydroxyvitamin D (ng/ml)				
Day 1	–0.03	0.14	–0.17 (–0.34, 0.00)	.06
Day 7	0.33	0.69	–0.37 (–0.60, –0.13)	.002
Day 8	0.18	0.69	–0.51 (–0.80, –0.21)	< .001
Day 14	0.14	0.94	–0.80 (–1.11, –0.49)	< .001
Day 21	0.10	0.75	–0.64 (–1.01, –0.28)	< .001
Day 35	0.03	0.62	–0.59 (–0.94, –0.23)	.001
Alkaline phosphatase (IU/l)				
Day 1	0.3	0.4	–0.1 (–3.9,3.7)	.96
Day 7	1.6	2.5	–0.9 (–5.5,3.7)	.69
Day 8	2.9	6.6	–3.6 (–8.4,1.2)	.14
Day 14	1.4	5.6	–4.2 (–9.8,1.3)	.13
Day 21	0.3	8.7	–8.4 (–14.2, –2.6)	.005
Day 35	2.3	9.6	–7.3 (–13.7, –0.9)	.03
Bone-specific alkaline phosphatase (µg/l)				
Day 1	0.4	0.3	0.1 (–0.4,0.7)	.67
Day 7	–0.1	0.6	–0.7 (–1.3,–0.1)	.03
Day 8	0.0	1.3	–1.3 (–2.1, –0.5)	.002
Day 14	–0.1	0.8	–1.0 (–2.0,0.1)	.07
Day 21	–0.1	1.5	–1.6 (–2.7, –0.6)	.003
Day 35	0.5	2.3	–1.8 (–2.8,–0.7)	< .001
N-terminal propeptide of Type I collagen (ng/ml)				
Day 1	–1.8	–2.0	0.2 (–3.6,3.9)	.92
Day 7	–7.0	–11.8	4.8 (0.7,8.9)	.02
Day 8	–6.7	–11.4	4.7 (0.4,8.9)	.03
Day 14	–4.9	–19.5	14.6 (9.2,20.1)	< .001
Day 21	–2.2	–17.3	15.1 (9.6,20.5)	< .001
Day 35	–1.7	–11.4	9.7 (3.9,15.5)	.001
Carboxy-terminal collagen crosslinks (ng/ml)				
Day 1	0.05	–0.01	0.05 (0.01,0.10)	.01
Day 7	0.00	–0.04	0.05 (0.01,0.09)	.02
Day 8	0.03	–0.05	0.08 (0.04,0.12)	< .001
Day 14	0.02	–0.06	0.08 (0.04,0.13)	< .001
Day 21	0.06	–0.04	0.10 (0.05,0.15)	< .001
Day 35	0.05	0.00	0.05 (–0.01, 0.10)	0.10

Data presented are for the safety analysis set.

Estimates are derived from a mixed model for repeated measurements with treatment, day, treatment-by-day interaction, and randomized strata as fixed effects, and baseline value and baseline value-by-day interactions as covariates.

CI, confidence interval; FCM, ferric carboxymaltose; FGF23, fibroblast growth factor; IIM, iron isomaltoside 1000/ferric derisomaltose.

Trial B

Biochemical/bone marker	IIM	FCM	Difference between IIM and FCM (95% CI)	P Value
Serum phosphate (mg/dl)				
Day 1	0.23	–0.23	0.46 (0.30, 0.62)	< .001
Day 7	–0.38	–0.92	0.54 (0.32, 0.76)	< .001
Day 8	–0.40	–1.13	0.73 (0.49,0.96)	< .001
Day 14	–0.28	–1.50	1.22 (0.99,1.46)	< .001
Day 21	–0.05	–1.30	1.24 (0.98,1.51)	< .001
Day 35	0.15	–1.02	1.17 (0.91,1.43)	< .001
Fractional urinary excretion of phosphate (%)				
Day 1	0.3	1.7	–1.4 (–3.5,0.8)	.21
Day 7	1.2	5.0	–3.9 (–6.4,–1.3)	.004
Day 8	2.2	6.4	–4.2 (–6.7,–1.7)	.001
Day 14	–0.2	8.4	–8.6 (–12.0, –5.2)	< .001
Day 21	–0.0	6.5	–6.5 (–9.2,–3.8)	< .001
Day 35	1.0	5.3	–4.3 (–7.4,–1.2)	.007
Intact FGF23 (pg/ml)				
Day 1	–4.6	92.3	–96.8 (–119.8, –73.8)	< .001
Day 7	17.1	32.8	–15.7 (–34.9, 3.4)	.11
Day 8	6.2	257.9	–251.7 (–307.2, –196.2)	< .001
Day 14	–5.9	73.2	–79.1 (–103.7, –54.5)	< .001
Day 21	–8.5	53.3	–61.8 (–83.0, –40.5)	< .001
Day 35	–8.7	9.3	–18.0 (–30.1, –5.9)	.004
C-terminal FGF23 (RU/ml)				
Day 1	–796.2	–738.7	–57.5 (–131.1, 16.1)	.12
Day 7	–807.2	–827.9	20.7 (–49.7, 91.0)	.55
Day 8	–816.7	–661.0	–155.7 (–234.7, –76.6)	< .001
Day 14	–835.8	–808.5	–27.3 (–86.0, 31.5)	.35
Day 21	–848.2	–823.9	–24.3 (–62.3, 13.7)	.20
Day 35	–840.9	–852.2	11.3 (–18.6, 41.2)	.44
Ionized calcium (mg/dl)				
Day 1	0.01	0.04	–0.03 (–0.10, 0.03)	.30
Day 7	0.04	–0.01	0.05 (–0.02, 0.13)	.16
Day 8	0.02	–0.03	0.05 (–0.02, 0.12)	.13
Day 14	–0.08	–0.07	–0.01 (–0.17, 0.16)	.94
Day 21	0.04	–0.03	0.07 (0.00,0.14)	.04
Day 35	0.02	–0.02	0.05 (–0.03, 0.12)	.24
Parathyroid hormone (pg/ml)				
Day 1	–0.9	–5.5	4.6 (–2.7,11.9)	.22
Day 7	–2.5	2.2	–4.6 (–13.5,4.2)	.30
Day 8	–1.9	–2.3	0.4 (–7.8,8.6)	.92
Day 14	6.9	22.6	–15.7 (–26.1, –5.3)	.003
Day 21	0.8	23.3	–22.5 (–33.9, –11.2)	< .001
Day 35	–1.8	23.0	–24.8 (–35.4, –14.2)	< .001

Biochemical/bone marker	IIM	FCM	Difference between IIM and FCM (95% CI)	P Value
25-Hydroxyvitamin D (ng/ml)				
Day 1	–0.5	–0.3	–0.2 (–1.1, 0.7)	.69
Day 7	–0.4	0.6	–1.0 (–2.3, 0.2)	.10
Day 8	–0.9	0.8	–1.6 (–3.0, –0.3)	.02
Day 14	–1.2	0.7	–1.9 (–3.5, –0.3)	.02
Day 21	–1.3	0.1	–1.4 (–3.0, 0.3)	.10
Day 35	–0.3	–0.5	0.1 (–1.8, 2.0)	.89
1,25-Dihydroxyvitamin D (pg/ml)				
Day 1	5.4	–16.5	21.8 (17.7, 26.0)	< .001
Day 7	–17.9	–22.5	4.6 (–4.1, 13.3)	.29
Day 8	–14.0	–33.5	19.6 (12.4, 26.7)	< .001
Day 14	–1.4	–34.5	33.1 (26.0, 40.1)	< .001
Day 21	–0.9	–22.7	21.8 (14.2, 29.4)	< .001
Day 35	–0.6	–9.7	9.0 (1.2, 16.9)	.03
24,25-Dihydroxyvitamin D (ng/ml)				
Day 1	0.02	0.08	–0.06 (–0.22, 0.11)	.51
Day 7	0.30	0.26	0.04 (–0.24, 0.32)	.76
Day 8	0.24	0.38	–0.14 (–0.41, 0.14)	.32
Day 14	0.09	0.56	–0.47 (–0.76, –0.18)	.002
Day 21	0.00	0.51	–0.50 (–0.77, –0.24)	< .001
Day 35	0.01	0.23	–0.23 (–0.50, 0.05)	.11
Alkaline phosphatase (IU/l)				
Day 1	0.4	1.4	–1.0 (–3.0, 1.0)	.32
Day 7	0.7	2.4	–1.7 (–4.5, 1.1)	.22
Day 8	0.8	3.6	–2.8 (–6.1, 0.4)	.08
Day 14	–0.5	4.5	–5.0 (–10.0, –0.0)	.05
Day 21	–0.4	5.2	–5.6 (–13.3, 2.2)	.16
Day 35	1.1	6.9	–5.8 (–11.2, –0.3)	.04
Bone-specific alkaline phosphatase (µg/l)				
Day 1	–0.0	0.3	–0.4 (–1.2, 0.4)	.34
Day 7	–0.2	0.3	–0.5 (–1.1, 0.1)	.10
Day 8	–0.3	0.6	–0.9 (–1.7, –0.1)	.03
Day 14	–0.3	1.1	–1.3 (–2.4, –0.3)	.01
Day 21	–0.2	1.2	–1.4 (–2.5, –0.3)	.01
Day 35	–0.1	2.1	–2.3 (–3.2, –1.3)	< .001
N-terminal propeptide of Type I collagen (ng/ml)				
Day 1	–3.4	–4.9	1.5 (–1.7, 4.7)	.35
Day 7	–10.0	–10.5	0.5 (–3.9, 4.9)	.83
Day 8	–9.5	–12.4	2.9 (–1.4, 7.1)	.18
Day 14	–9.4	–16.4	6.9 (3.2, 10.7)	< .001
Day 21	–5.3	–15.4	10.1 (4.7, 15.5)	< .001
Day 35	–2.8	–11.2	8.3 (1.8, 14.8)	.01
Carboxy-terminal collagen crosslinks (ng/ml)				
Day 1	0.03	–0.03	0.06 (0.01, 0.11)	.01
Day 7	–0.01	–0.04	0.02 (–0.03, 0.08)	.34
Day 8	0.00	–0.09	0.09 (0.04, 0.14)	< .001
Day 14	–0.02	–0.06	0.04 (–0.00, 0.09)	.06
Day 21	0.01	–0.03	0.04 (–0.01, 0.09)	.15
Day 35	0.01	0.02	–0.01 (–0.06, 0.04)	.74

Data presented are for the safety analysis set.

Estimates are derived from a mixed model for repeated measurements with treatment, day, treatment-by-day interaction, and randomized strata as fixed effects, and baseline value and baseline value-by-day interactions as covariates.

CI, confidence interval; FCM, ferric carboxymaltose; FGF23, fibroblast growth factor; IIM, iron isomaltoside 1000/ferric derisomaltose.

Pooled data for Trial A and Trial B

Biochemical/bone marker	IIM	FCM	Difference between IIM and FCM (95% CI)	P Value
Serum phosphate (mg/dl)				
Day 1	0.24	–0.23	0.47 (0.36, 0.58)	< .001
Day 7	–0.22	–1.03	0.81 (0.66, 0.96)	< .001
Day 8	–0.25	–1.13	0.88 (0.72,1.04)	< .001
Day 14	–0.18	–1.46	1.29 (1.12,1.46)	< .001
Day 21	–0.02	–1.15	1.13 (0.94,1.33)	< .001
Day 35	0.18	–0.96	1.14 (0.96,1.32)	< .001
Fractional urinary excretion of phosphate (%)				
Day 1	–0.7	2.1	–2.8 (–4.2,–1.3)	< .001
Day 7	0.9	6.7	–5.7 (–7.9,–3.6)	< .001
Day 8	1.7	7.8	–6.1 (–8.4,–3.7)	< .001
Day 14	0.2	9.9	–9.7 (–12.6, –6.9)	< .001
Day 21	0.2	7.8	–7.6 (–10.2, –5.1)	< .001
Day 35	–0.3	5.0	–5.3 (–7.7,–2.9)	< .001
Intact FGF23 (pg/ml)				
Day 1	–3.9	98.4	–102.2 (–119.1, –85.4)	< .001
Day 7	12.8	51.3	–38.6 (–53.4, –23.8)	< .001
Day 8	7.8	282.2	–274.4 (–320.1, –228.6)	< .001
Day 14	–6.6	92.1	–98.7 (–119.2, –78.2)	< .001
Day 21	–5.2	61.4	–66.6 (–84.8, –48.5)	< .001
Day 35	–8.3	20.1	–28.4 (–39.1, –17.6)	< .001
C-terminal FGF23 (RU/ml)				
Day 1	–688.4	–606.0	–82.4 (–122.1, –42.6)	< .001
Day 7	–704.3	–682.9	–21.4 (–50.2, 7.4)	.14
Day 8	–702.4	–525.4	–177.0 (–217.6, –136.4)	< .001
Day 14	–721.0	–653.6	–67.4 (–97.9, –36.9)	< .001
Day 21	–728.7	–690.1	–38.6 (–57.7, –19.5)	< .001
Day 35	–721.6	–714.7	–6.9 (–22.9,9.2)	.40
Ionized calcium (mg/dl)				
Day 1	0.03	0.02	0.00 (–0.04. 0.05)	.87
Day 7	0.03	–0.04	0.07 (0.03,0.12)	.003
Day 8	0.03	–0.03	0.06 (0.01,0.10)	.01
Day 14	–0.02	–0.08	0.05 (–0.03, 0.14)	.21
Day 21	0.05	–0.03	0.09 (0.04,0.14)	< .001
Day 35	0.02	–0.03	0.05 (-0.00, 0.10)	.06
Parathyroid hormone (pg/ml)				
Day 1	–0.9	–2.8	1.9 (–3.0,6.8)	.44
Day 7	–2.9	4.3	–7.2 (–13.5, –1.0)	.02
Day 8	–0.1	0.1	–0.3 (–6.7,6.1)	.93
Day 14	5.9	19.7	–13.8 (–21.6, –6.0)	< .001
Day 21	–0.9	20.1	–21.1 (–28.8, –13.4)	< .001
Day 35	–0.3	22.6	–22.8 (–31.1, –14.6)	< .001

Biochemical/bone marker	IIM	FCM	Difference between IIM and FCM (95% CI)	P Value
25-Hydroxyvitamin D (ng/ml)				
Day 1	–0.2	0.0	–0.2 (–0.8,0.4)	.46
Day 7	0.2	–0.2	0.4 (–0.5,1.4)	.35
Day 8	–0.2	0.3	–0.6 (–1.6,0.5)	.30
Day 14	–0.1	–0.4	0.2 (–1.0,1.5)	.71
Day 21	–0.4	–0.4	0.0 (–1.3,1.3)	1.0
Day 35	–0.4	–0.4	–0.1 (–1.4,1.3)	.94
1,25-Dihydroxyvitamin D (pg/ml)				
Day 1	4.8	–18.3	23.1 (19.7,26.5)	< .001
Day 7	–19.7	–30.0	10.3 (4.7,15.8)	< .001
Day 8	–15.8	–35.7	19.8 (14.5,25.2)	< .001
Day 14	–3.4	–36.1	32.7 (27.9, 37.6)	< .001
Day 21	–2.9	–25.3	22.4 (17.0,27.9)	< .001
Day 35	–3.2	–13.1	9.9 (4.7,15.1)	< .001
24,25-Dihydroxyvitamin D (ng/ml)				
Day 1	–0.00	0.11	–0.11 (–0.23, 0.01)	.07
Day 7	0.31	0.50	–0.20 (–0.38, –0.01)	.04
Day 8	0.20	0.56	–0.36 (–0.56, –0.15)	< .001
Day 14	0.12	0.77	–0.65 (–0.86, –0.44)	< .001
Day 21	0.06	0.64	–0.58 (–0.80, –0.36)	< .001
Day 35	0.02	0.44	–0.43 (–0.66, –0.20)	< .001
Alkaline phosphatase (IU/l)				
Day 1	0.4	0.9	–0.5 (–2.7,1.7)	.64
Day 7	1.1	2.6	–1.5 (–4.2,1.3)	.29
Day 8	1.8	5.2	–3.4 (–6.3,–0.5)	.02
Day 14	0.3	5.3	–5.0 (–8.8, –1.1)	.01
Day 21	–0.7	7.5	–8.2 (–13.4, –2.9)	.003
Day 35	1.4	8.6	–7.1 (–11.5, –2.8)	.002
Bone-specific alkaline phosphatase (µg/l)				
Day 1	0.2	0.3	–0.1 (–0.6,0.4)	.62
Day 7	–0.2	0.4	–0.6 (–1.0,–0.1)	.01
Day 8	–0.1	1.0	–1.1 (–1.7, –0.5)	< .001
Day 14	–0.2	1.0	–1.2 (–1.9,–0.4)	.002
Day 21	–0.2	1.3	–1.5 (–2.3, –0.8)	< .001
Day 35	0.2	2.2	–2.0 (–2.7,–1.3)	< .001
N-terminal propeptide of Type I collagen (ng/ml)				
Day 1	–2.3	–3.5	1.2 (–1.4,3.7)	.36
Day 7	–8.5	–11.2	2.7 (–0.2,5.7)	.07
Day 8	–8.1	–11.9	3.8 (0.8,6.7)	.01
Day 14	–7.1	–18.0	10.9 (7.5,14.2)	< .001
Day 21	–3.8	–16.3	12.5 (8.6,16.3)	< .001
Day 35	–2.4	–11.2	8.8 (4.5,13.1)	< .001
Carboxy-terminal collagen crosslinks (ng/ml)				
Day 1	0.04	–0.02	0.07 (0.03,0.10)	< .001
Day 7	–0.00	–0.04	0.03 (0.00,0.07)	.04
Day 8	0.02	–0.07	0.09 (0.06,0.12)	< .001
Day 14	0.01	–0.06	0.07 (0.04,0.10)	< .001
Day 21	0.04	–0.03	0.07 (0.04,0.10)	< .001
Day 35	0.03	0.01	0.02 (–0.02, 0.06)	.23

Data presented are for the safety analysis set.

Estimates are derived from a mixed model for repeated measurements with treatment, day, treatment-by-day interaction, trial, and randomized strata as fixed effects, and baseline value and baseline value-by-day interactions as covariates.

CI, confidence interval; FCM, ferric carboxymaltose; FGF23, fibroblast growth factor; IIM, iron isomaltoside 1000/ferric derisomaltose.

eTable 7. Secondary Efficacy End Points – Trial A, Trial B, and Pooled Data for Trial A and Trial B

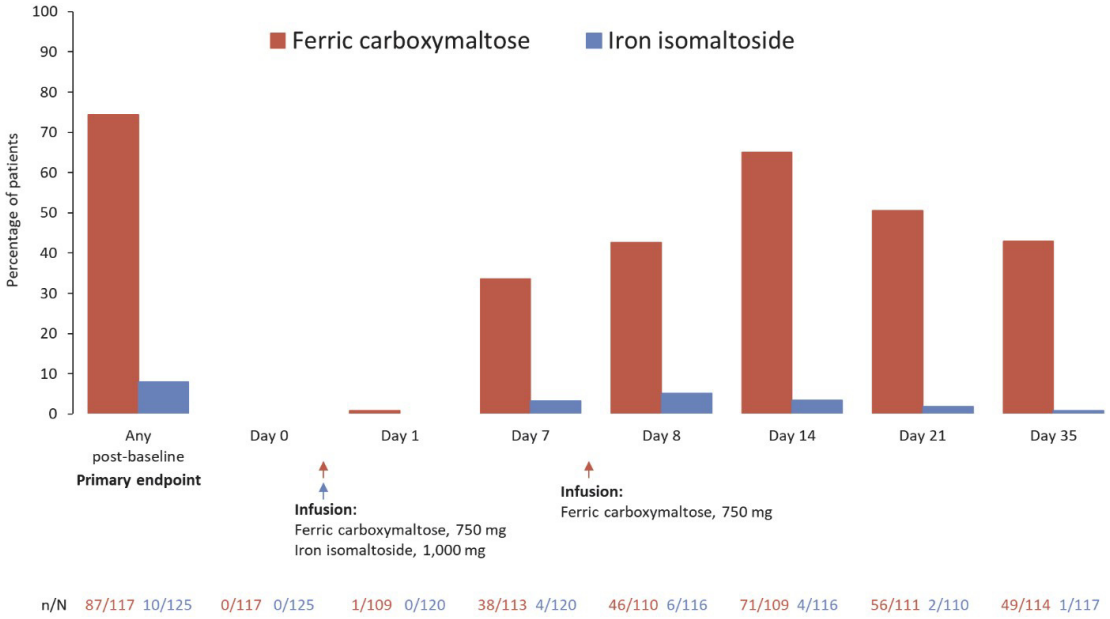
End point		Day 0 Mean (SD) n	1 Mean (SD) n	7 Mean (SD) n	8 Mean (SD) n	14 Mean (SD) n	21 Mean (SD) n	35 Mean (SD) n
Trial A								
Hemoglobin per gram of iron in actual dose (g/dl)[a,b]	IIM	–	–0.3 (1.2) (n=46)	0.6 (0.9) (n=48)	0.5 (1.2) (n=47)	1.5 (1.5) (n=48)	1.6 (1.4) (n=47)	2.1 (1.6) (n=49)
	FCM	–	0.3 (2.0) (n=42)	0.9 (1.6) (n=47)	0.6 (0.8) (n=45)	1.1 (0.9) (n=45)	1.4 (0.9) (n=46)	1.9 (1.0) (n=45)
	P	–	*P* = .24	*P* = .24	*P* = .74	*P* = .09	*P* = .009	*P* = .11
Hemoglobin (g/dl) (exploratory end point)	IIM	9.8 (1.3) (n=62)	9.7 (1.2) (n=54)	10.5 (0.9) (n=54)	10.4 (0.8) (n=54)	11.3 (1.1) (n=53)	11.6 (0.8) (n=53)	12.1 (1.0) (n=56)
	FCM	9.6 (1.3) (n=61)	9.8 (1.8) (n=52)	10.3 (1.2) (n=58)	10.6 (1.2) (n=55)	11.4 (1.0) (n=54)	11.9 (1.0) (n=56)	12.5 (1.1) (n=56)
	P	–	*P* = .37	*P* = .73	*P* = .12	*P* = .46	*P* = .24	*P* = .01
Ferritin (ng/ml)	IIM	15.7 (31.7) (n=62)	97.0 (52.0) (n=58)	277.3 (173.2) (n=59)	264.8 (171.3) (n=57)	149.9 (98.4) (n=57)	111.0 (122.3) (n=55)	63.4 (54.0) (n=58)
	FCM	11.7 (29.4) (n=61)	108.1 (80.1) (n=58)	301.3 (170.4) (n=59)	337.5 (214.5) (n=59)	364.6 (216.1) (n=57)	191.3 (126.4) (n=57)	120.6 (103.3) (n=59)
	P	–	*P* = .19	*P* = .56	*P* = .05	*P* < .001	*P* = .001	*P* < .001
Transferrin saturation (%)	IIM	16.6 (31.2) (n=61)	136.6 (41.9) (n=58)	27.4 (14.1) (n=59)	24.1 (13.0) (n=57)	22.2 (10.3) (n=57)	22.3 (14.0) (n=55)	20.8 (10.2) (n=57)
	FCM	7.0 (6.7) (n=60)	94.2 (36.1) (n=58)	20.0 (12.5) (n=59)	68.2 (40.0) (n=59)	23.5 (9.1) (n=57)	23.8 (9.9) (n=56)	21.7 (9.3) (n=59)
	P	–	*P* < .001	*P* = .009	*P* < .001	*P* = .37	*P* = .48	*P* = .36
Trial B								
Hemoglobin per gram of iron in actual dose (g/dl)[a,b]	IIM	–	0.2 (0.8) (n=48)	1.0 (1.1) (n=51)	1.1 (1.2) (n=51)	1.7 (1.1) (n=53)	1.9 (0.9) (n=53)	2.2 (1.2) (n=54)
	FCM	–	0.5 (1.2) (n=47)	1.4 (1.1) (n=51)	0.8 (0.7) (n=51)	1.3 (0.9) (n=53)	1.6 (0.9) (n=54)	2.0 (0.9) (n=53)
	P	–	*P* = .08	*P* = .17	*P* = .06	*P* = .004	*P* = .02	*P* = .10
Hemoglobin (g/dl) (exploratory end point)	IIM	9.6 (1.2) (n=61)	9.7 (1.4) (n=54)	10.6 (1.5) (n=57)	10.6 (1.5) (n=56)	11.3 (1.3) (n=56)	11.4 (1.2) (n=56)	11.8 (1.4) (n=57)
	FCM	9.3 (1.4) (n=61)	9.6 (1.7) (n=50)	10.4 (1.4) (n=54)	10.5 (1.4) (n=54)	11.3 (1.1) (n=55)	11.8 (1.0) (n=57)	12.3 (1.2) (n=56)
	P	–	*P* = .23	*P* = .99	*P* = .66	*P* = .42	*P* = .003	*P* = .001

End point		Day 0 Mean (SD) n	Day 1 Mean (SD) n	Day 7 Mean (SD) n	Day 8 Mean (SD) n	Day 14 Mean (SD) n	Day 21 Mean (SD) n	Day 35 Mean (SD) n
Trial B (continued)								
Ferritin (ng/ml)	IIM	10.5 (13.4) (n=61)	84.3 (82.9) (n=60)	263.0 (165.4) (n=60)	230.1 (150.4) (n=58)	154.8 (101.8) (n=57)	109.4 (95.1) (n=56)	66.7 (74.2) (n=57)
	FCM	17.9 (40.5) (n=61)	101.1 (83.7) (n=57)	297.9 (214.6) (n=57)	332.5 (227.7) (n=56)	398.2 (279.5) (n=57)	251.3 (213.9) (n=57)	144.9 (164.0) (n=57)
	P	–	*P* = .66	*P* = .49	*P* = .01	*P* < .001	*P* < .001	*P* = .004
Transferrin saturation (%)	IIM	8.4 (8.1) (n=61)	132.3 (48.8) (n=60)	23.5 (9.8) (n=60)	20.9 (9.3) (n=58)	18.9 (7.6) (n=56)	19.2 (9.2) (n=56)	18.3 (10.5) (n=57)
	FCM	9.2 (10.0) (n=59)	99.3 (33.1) (n=56)	22.3 (28.6) (n=57)	83.0 (29.3) (n=56)	26.2 (12.1) (n=57)	25.5 (9.8) (n=56)	23.9 (11.3) (n=56)
	P	–	*P* = .05	*P* = .58	*P* < .001	*P* < .001	*P* < .001	*P* = .004
Pooled data for Trial A and Trial B								
Hemoglobin per gram of iron in actual dose (g/dl)[a,b]	IIM	–	–0.0 (1.1) (n=94)	0.8 (1.0) (n=99)	0.8 (1.2) (n=98)	1.6 (1.3) (n=101)	1.8 (1.2) (n=100)	2.2 (1.4) (n=103)
	FCM	–	0.4 (1.6) (n=89)	1.2 (1.4) (n=98)	0.7 (0.7) (n=96)	1.2 (0.9) (n=98)	1.5 (0.9) (n=100)	2.0 (0.9) (n=98)
	P	–	*P* = .01	*P* = .09	*P* = .08	*P* < .001	*P* < .001	*P* = .02
Hemoglobin (g/dl) (exploratory end point)	IIM	9.7 (1.3) (n=123)	9.7 (1.3) (n=108)	10.5 (1.2) (n=111)	10.5 (1.2) (n=110)	11.3 (1.2) (n=109)	11.5 (1.0) (n=109)	11.9 (1.2) (n=113)
	FCM	9.5 (1.4) (n=122)	9.7 (1.7) (n=102)	10.3 (1.3) (n=112)	10.6 (1.3) (n=109)	11.3 (1.1) (n=109)	11.8 (1.0) (n=113)	12.4 (1.1) (n=112)
	P	–	*P* = .08	*P* = .72	*P* = .24	*P* = .50	*P* = .003	*P* < .001
Ferritin (ng/ml)	IIM	13.1 (24.4) (n=123)	90.5 (69.4) (n=118)	270.1 (168.7) (n=119)	247.3 (161.4) (n=115)	152.4 (99.7) (n=114)	110.2 (108.9) (n=111)	65.0 (64.5) (n=115)
	FCM	14.8 (35.4) (n=122)	104.6 (81.6) (n=115)	299.6 (192.6) (n=116)	335.1 (220.1) (n=115)	381.4 (249.3) (n=114)	221.3 (177.5) (n=114)	132.6 (136.5) (n=116)
	P	–	*P* = .25	*P* = .27	*P* < .001	*P* < .001	*P* < .001	*P* < .001
Transferrin saturation (%)	IIM	12.5 (23.1) (n=122)	134.4 (45.4) (n=118)	25.4 (12.2) (n=119)	22.5 (11.4) (n=115)	20.6 (9.1) (n=113)	20.7 (11.8) (n=111)	19.5 (10.4) (n=114)
	FCM	8.1 (8.5) (n=119)	96.7 (34.6) (n=114)	21.1 (21.9) (n=116)	75.4 (35.8) (n=115)	24.8 (10.7) (n=114)	24.7 (9.8) (n=112)	22.8 (10.3) (n=115)
	P	–	*P* < .001	*P* = .11	*P* < .001	*P* < .001	*P* = .004	*P* = .003

Data are presented for the randomized analysis set, unless otherwise stated as [a] all patients in the randomized data set, who received at least one dose of trial drug, had at least one post-baseline hemoglobin assessment, and who did not have a major protocol deviation. [b] Values are mean (SD) change in hemoglobin.

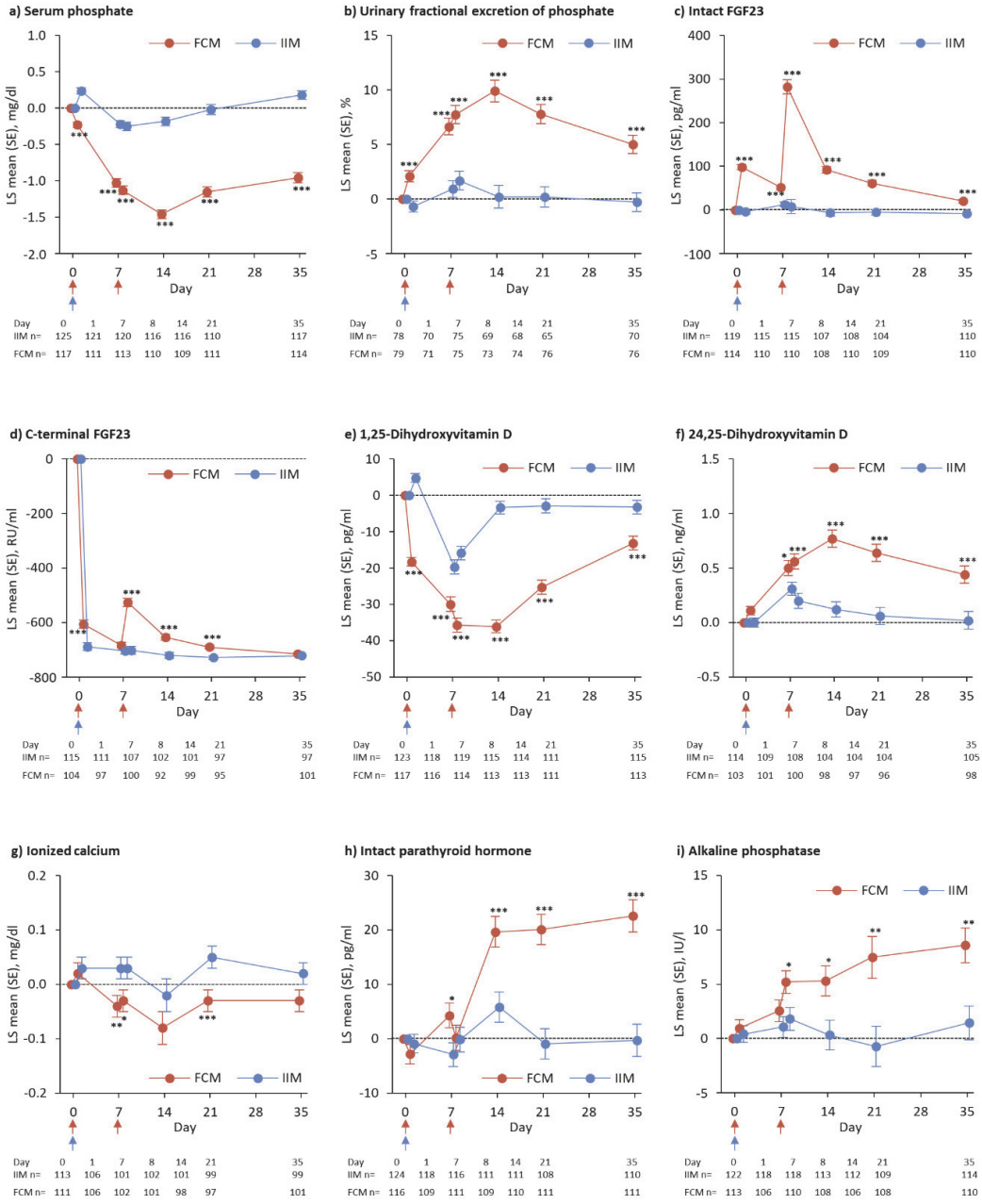
P values are for between-group comparisons from a mixed model for repeated measures analysis with treatment, day, treatment-by-day, trial (in the pooled analysis) and stratum as fixed effects and baseline value and baseline value-by-day, as covariates. FCM, ferric carboxymaltose; IIM, iron isomaltoside 1000/ferric derisomaltose; SD, standard deviation.

eFigure 1. Incidence of Hypophosphatemia (Serum Phosphate <2.0 mg/dl) Overall and Prevalence of Hypophosphatemia at Each Time Point – Pooled Data for Trial A and Trial B



The leftmost columns correspond to the primary outcome of incident hypophosphatemia at any time during the trial. The remaining columns correspond to the proportions of patients with serum phosphate <2.0 mg/dl at each individual time point.
Safety analysis set.

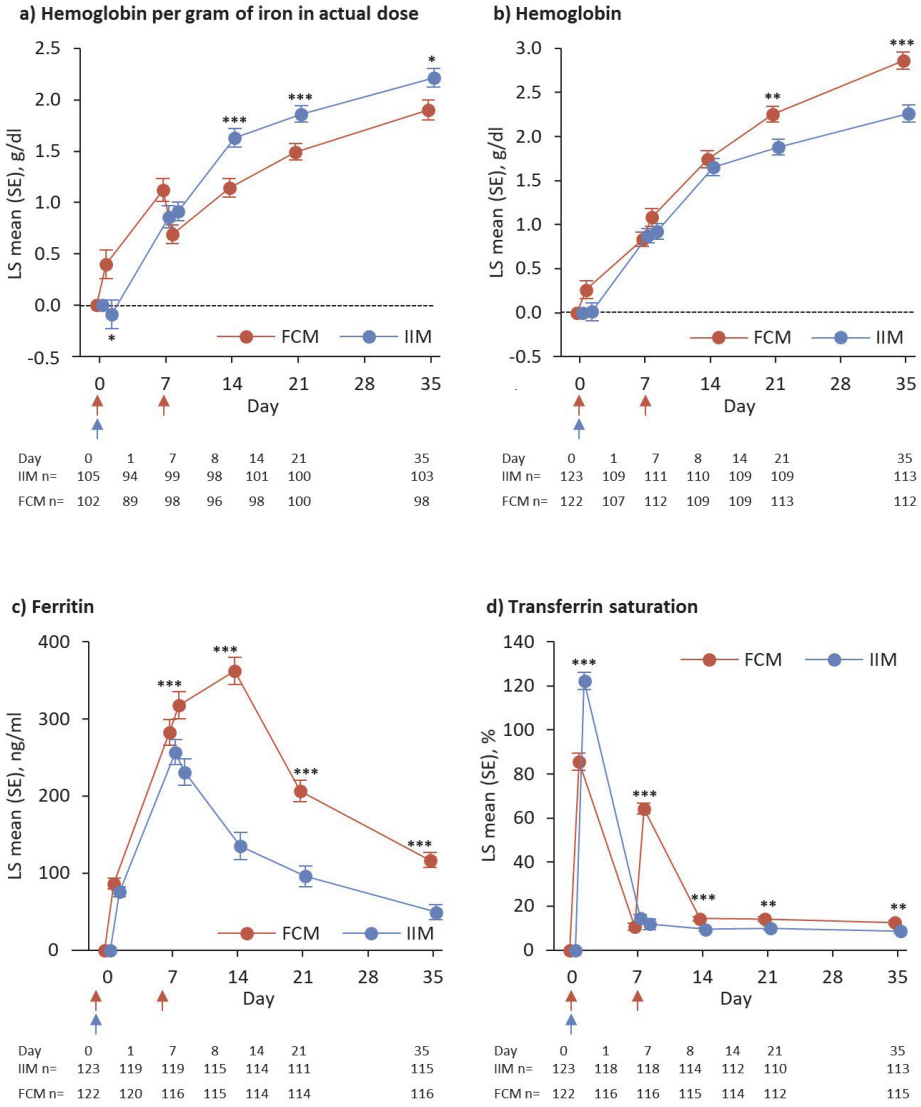
eFigure 2. Least Squares Mean Changes From Baseline in Biomarkers of Mineral and Bone Homeostasis According to Iron Treatment – Pooled Data for Trial A andTrial B



Red arrows indicate infusion of ferric carboxymaltose, 750 mg; blue arrows indicate infusion of iron isomaltoside, 1000 mg.
*$P < .05$, **$P < .01$, ***$P < .001$ between-group comparisons from a mixed model for repeated measures analysis with treatment, day, treatment-by-day, trial and stratum as fixed effects and baseline value and baseline value-by-day as covariates; safety analysis set.

FCM, ferric carboxymaltose; FGF23, fibroblast growth factor 23; IIM iron isomaltoside 1000/ferric derisomaltose; LS, least squares; SE, standard error.

eFigure 3. Least Squares Mean Changes From Baseline in Iron Parameters – Pooled Data for Trial A and Trial B



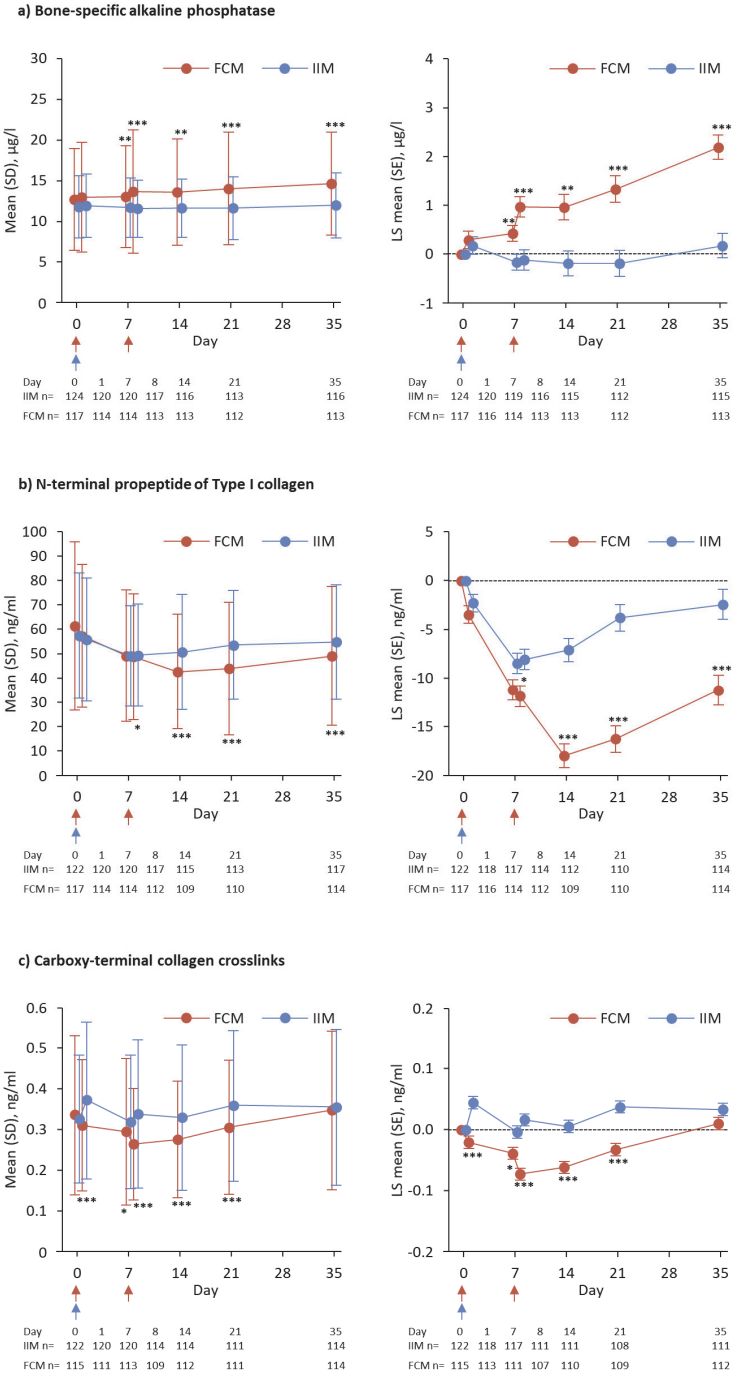
Red arrows indicate infusion of FCM, 750 mg; blue arrows indicate infusion of IIM, 1000 mg.

*$P < .05$, **$P < .01$, ***$P < .001$ between-group comparison from a mixed model for repeated measurements with treatment, day, treatment-by-day, trial and stratum as fixed effects, and baseline value and baseline value-by-day as covariates; randomized data set; part a) is all patients in the randomized data set, who received at least one dose of trial drug, had at least one post baseline hemoglobin assessment, and who did not have a major protocol deviation.

Transferrin saturation was calculated as: [total serum iron (µmol/l) * 5.586] / [transferrin (g/l) *100] * 70.9. In accordance with the pharmacokinetics of IIM, on day 1 after the infusion of 1000 mg of the drug, when TSAT was >100%, a proportion of the drug was still present in the circulation and this is also measured with the serum iron assay and causes the calculated TSAT to exceed 100%.

FCM, ferric carboxymaltose; IIM iron isomaltoside 1000/ferric derisomaltose; LS, least squares; SE, standard error.

eFigure 4. Changes in Bone Turnover Markers – Pooled Data for Trial A and Trial B



Left-hand figures show mean absolute values; right-hand figures show LS mean change from baseline values.

Red arrows indicate infusion of FCM, 750 mg; blue arrows indicate infusion of IIM, 1000 mg.

*$P < .05$, **$P \leq .01$, ***$P < .001$ between-group comparison from a mixed model for repeated measures analysis with treatment, day, treatment-by-day, trial and stratum as fixed effects and baseline value and baseline value-by-day as covariates; safety analysis set.

FCM, ferric carboxymaltose; IIM, iron isomaltoside 1000/ferric derisomaltose; LS, least squares; SD, standard deviation; SE, standard error.