Supplementary material

Hypophosphataemia following ferric derisomaltose and ferric carboxymaltose in patients with iron deficiency anaemia due to inflammatory bowel disease (PHOSPHARE-IBD): A randomised clinical trial

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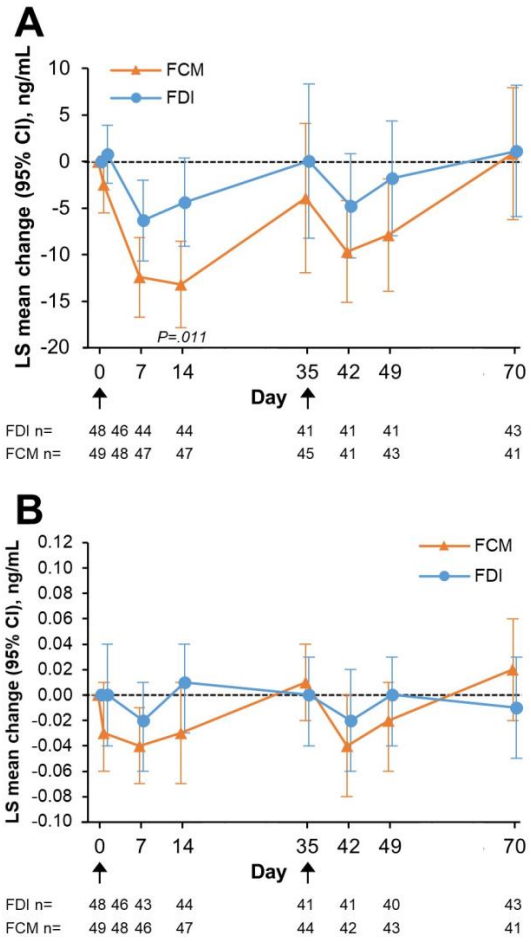
Figure S1: Change in additional bone biochemical parameters, according to IV iron treatment – (A) N-Terminal P1NP; (B) CTx



Data are presented for the safety analysis set. P-values are for between-group differences. Black arrows indicate infusion of IV iron (FDI or FCM). Due to lack of space, the x-axis Day 1 labels and tick marks are not shown. CI=confidence interval. CTx=C-terminal collagen crosslinks. FCM=ferric carboxymaltose. FDI=ferric derisomaltose. IV=intravenous. LS=least squares. P1NP=propeptide of type 1 collagen.

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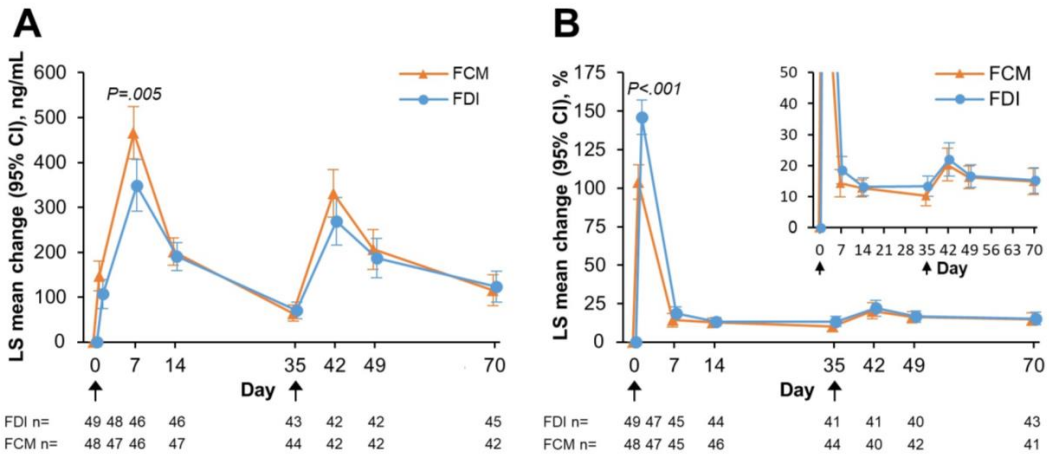
Figure S2: Changes from baseline in key anaemia and iron parameters, according to IV iron treatment – (A) Ferritin; (B) TSAT



Data are presented for the ITT analysis set. Black arrows indicate infusion of IV iron (FDI or FCM). Due to lack of space, the x-axis Day 1 labels and tick marks are not shown. Transferrin saturation was calculated as: [total serum iron (µmol/l) * 5.586] / [transferrin (g/l) *100] * 70.9. In accordance with the pharmacokinetics of FDI, 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. This is also measured with the serum iron assay and causes the calculated TSAT to exceed 100%. CI=confidence interval. FCM=ferric carboxymaltose. FDI=ferric derisomaltose. ITT=intention-to-treat. IV=intravenous. LS=least squares. TSAT=transferrin saturation.

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Table S1: Trial endpoints

Primary endpoint
1. Incidence of hypophosphataemia (defined as serum phosphate <2.0 mg/dL) at any time from baseline to Day 35.
Secondary safety endpoints
1. Incidence of hypophosphataemia at Days 1,7 14, 35, 42, 49, and 70.
2. Incidence of hypophosphataemia at any time from baseline to Day 70.
3. Incidence of serum phosphate ≤1.0 mg/dL at Days 1, 7, 14, 35, 42, 49, and 70.
4. Incidence of serum phosphate ≤1.0 mg/dL at any time from baseline to Day 35 and at any time from baseline to Day 70.
5. Time with hypophosphataemia (i.e., time with serum phosphate <2.0 mg/dL).
6. Absolute and relative changes in serum phosphate from baseline to Days 1, 7, 14, 35, 42, 49, and 70.
7. Change in fractional excretion of phosphate from baseline to Days 1, 7, 14, 35, 42, 49, and 70.
8. Change in iFGF23, cFGF23, Vitamin D (25-hydroxyvitamin D; 1,25-dihydroxyvitamin D; 24,25-dihydroxyvitamin D), PTH, and ionised calcium from baseline to Days 1, 7, 14, 35, 42, 49, and 70.
9. Type and incidence of AEs.
10. Serious or severe hypersensitivity reaction starting on or after the first dose of randomised treatment (i.e., treatment emergent). The hypersensitivity terms are defined as standardised Medical Dictionary for Regulatory Activities query terms (including four additional terms).
In addition, physical examinations and measurements of vital signs, height, weight, ECG, and safety laboratory parameters were measured as part of standard safety assessments.
Secondary efficacy endpoints
1. Change in Hb, serum ferritin, and TSAT from baseline to Days 1, 7, 14, 35, 42, 49, and 70.
Exploratory endpoints
1. Change in biochemical bone/muscle markers (N-terminal PINP, CTx, ALP [bone-specific and total], and creatine kinase) from baseline to Days 1, 7, 14, 35, 42, 49, and 70.
2. Change in fatigue symptoms from baseline to Days 14, 35, 49, and 70, measured by the FACIT Fatigue Scale.
3. Change in quality of life from baseline to Days 14, 35, 49, and 70, measured by Short Form-36 questionnaire.
4. Change in bone pain from baseline to Days 14, 35, 49, and 70, measured on a visual analogue scale.
5. Change in muscle strength from baseline to Days 14, 35, 49, and 70, measured by grip strength.
6. Change in upper and lower limb proximal muscle function from baseline to Days 14, 35, 49, and 70, measured by the '1 kg arm lift' test and the '30 sec chair stand' test.
7. Change in respiratory muscles strength from baseline to Days 14, 35, 49, and 70, measured by MIP and MEP.
8. Change in disease activity status using Harvey-Bradshaw Index for Crohn's disease or Partial Mayo Score (excluding Endoscopy sub-score) for ulcerative colitis from baseline to Days 35 and 70.

AE=adverse event. ALP=alkaline phosphatase. cFGF23=C-terminal fibroblast growth factor 23. CTx=C-terminal collagen crosslinks. ECG=electrocardiogram. FACIT=Functional Assessment of Chronic Illness Therapy. Hb=haemoglobin. iFGF23=intact fibroblast growth factor 23. MEP=Maximal Expiratory Pressure. MIP=Maximal Inspiratory Pressure. P1NP=propeptide of type 1 collagen. PTH=parathyroid hormone. TSAT=transferrin saturation.

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Table S2: Incidence of hypophosphataemia (primary and secondary safety endpoints)

	FDI (N=48)	FCM (N=49)	Risk difference (95% CI)	p-value
Primary safety endpoint, n (%)				
Incidence of hypophosphataemia at any time from baseline to Day 35[a]	4 (8.3%)	25 (51.0%)	-42.8% (-57.1, -24.6)	<0.0001
Secondary safety endpoints: Incidence of hypophosphataemia, n (%)				
At any time from baseline to Day 70[a]	6 (12.5%)	29 (59.2%)	-46.6% (-60.9, -28.1)	<0.0001
At Day 1[b]	0 (0.0%) (n=45)	1 (2.1%) (n=48)	-2.1% (-6.1, 2.0)	0.3329
At Day 7[a]	1 (2.2%) (n=45)	20 (42.6%) (n=47)	-40.3% (-54.6, -23.1)	<0.0001
At Day 14[a]	1 (2.2%) (n=45)	22 (45.8%) (n=48)	-43.6% (-57.6, -26.2)	<0.0001
At Day 35[a]	1 (2.4%) (n=41)	2 (4.4%) (n=45)	-2.0% (-14.2, 10.5)	0.6092
At Day 42[b]	0 (0.0%) (n=42)	18 (41.9%) (n=43)	-41.9% (-56.6, -27.1)	<0.0001
At Day 49[a]	3 (7.3%) (n=41)	13 (29.5%) (n=44)	-22.5% (-38.0, -5.7)	0.0070
At Day 70[b]	0 (0.0%) (n=44)	2 (4.7%) (n=43)	-4.7% (-10.9, 1.6)	0.1502

Data are presented for the safety analysis set. For baseline to Day 35 (primary safety endpoint), two patients in the FDI group and one patient in the FCM group did not have a postbaseline observation and were, therefore, set as having hypophosphataemia. CI=confidence interval. FCM=ferric carboxymaltose. FDI=ferric derisomaltose. N=number of patients in analysis set. n=number of patients with observation. [a]Risk difference with 95% Newcombe CI adjusted for stratum using Cochran–Mantel–Haenszel method. [b]Unadjusted risk difference and 95% Wald CI presented

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Table S3: *Post hoc* sensitivity analyses for the primary endpoint

	FDI	FCM
Incidence of hypophosphataemia at any time from baseline to Day 35, n/N (%)		
Primary outcome: Imputes loss to follow-up as hypophosphataemia present	4/48 (8.3%)	25/49 (51.0%)
Post hoc analysis 1: Imputes loss to follow-up as hypophosphataemia absent	2/48 (4.2%)	24/49 (49.0%)
Post hoc analysis 2: Excludes patients lost to follow-up	2/46 (4.3%)	24/48 (50.0%)

Data are presented for the safety analysis set. Three patients lacked follow-up data on serum phosphate after having received IV iron (2/48 in the FDI group and 1/49 in the FCM group). FCM=ferric carboxymaltose. FDI=ferric derisomaltose.

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Table S4: Difference in LS mean change from baseline in FACIT Fatigue Scale score for Crohn's disease versus ulcerative colitis

	LS mean (95% CI)	p-value
Difference in LS mean change from baseline in FACIT Fatigue Scale score[a]		
At Day 14	4.10 (-3.21, 11.40)	0.2680
At Day 35	8.51 (0.66, 16.36)	0.0339
At Day 49	4.79 (-4.10, 13.68)	0.2874
At Day 70	5.29 (-3.54, 14.12)	0.2371

[a]FDI-FCM (Crohn's disease) vs FDI-FCM (Ulcerative colitis)

Data are presented for the ITT analysis set. CI=confidence interval. FACIT= Functional Assessment of Chronic Illness Therapy. FCM=ferric carboxymaltose. FDI=ferric derisomaltose. ITT=intention-to-treat. LS=least squares. MMRM=mixed model for repeated measures. Patients were grouped from both the FCM and FDI treatment arms. Estimates are from an MMRM model with treatment, day, diagnosis and stratum as factors, treatment-by-day-by-diagnosis and day-by-baseline value interactions, and baseline value as covariate

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