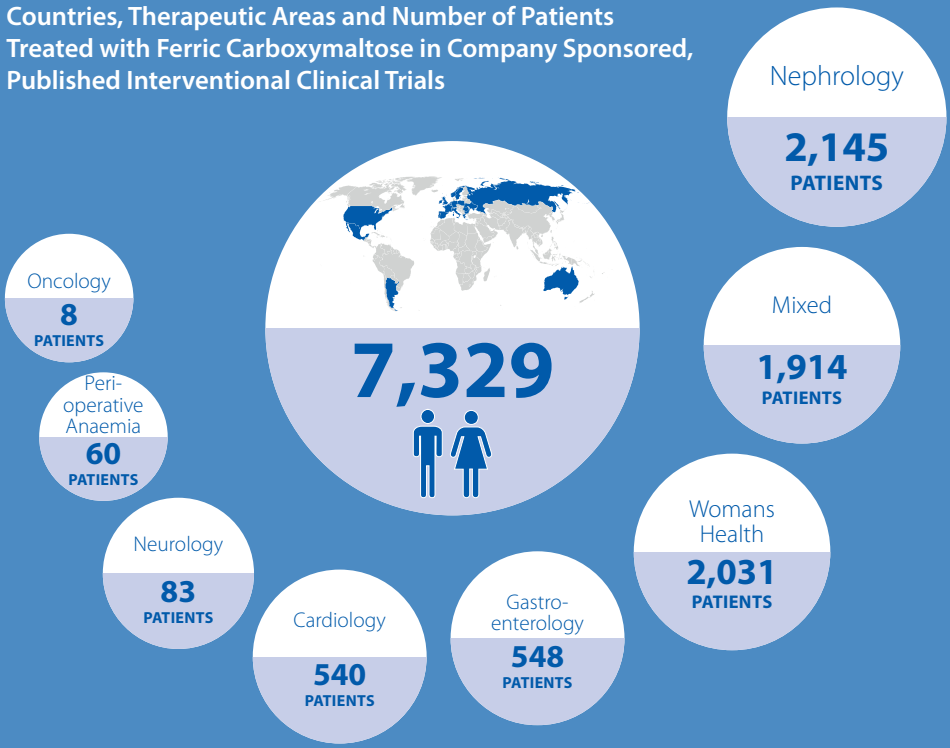
Clinical Compendium

Ferric Carboxymaltose

for the Treatment of Iron Deficiency (ID)

Countries, Therapeutic Areas and Number of Patients Treated with Ferric Carboxymaltose in Company Sponsored, Published Interventional Clinical Trials



May 2019

VIFOR PHARMA

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CF Barish et al. Anemia 2012; 2012: 172104

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JE Onken et al. Transfusion 2014; 54: 306–315

Abbreviations:

AE	adverse event
bid	*bis in die* (twice daily)
BNP	brain natriuretic peptide
CHF	chronic heart failure
CI	confidence interval
CGI	clinical global impression
CKD	chronic kidney disease
DEX	iron dextran
EQ-5D	European Quality of Life 5D questionnaire
ESA	erythropoiesis-stimulating agent
FAS	full analysis set
FCM	ferric carboxymaltose
FS	ferrous sulfate
GFR	glomerular filtration rate
Hb	hemoglobin
HD	hemodialysis
HF	heart failure
HR	hazard ratio
IBD	inflammatory bowel diseases
ID	iron deficiency
IDA	iron deficiency anemia
IRLS	International Restless Legs Scale
ITT	intention-to-treat
IV	intravenous(ly)
IS	iron sucrose
KCCQ	Kansas City Cardiomyopathy Questionnaire
LOCF	last observation carried forward
LSM	least-square means
LVEF	left ventricular ejection fraction
MOS	medical outcomes study
ND-CKD	nondialysis-dependent chronic kidney disease
NDD	non-dialysis-dependent
NT-proBNP	N-terminal pro brain natriuretic peptide
NYHA	New York Heart Association
OR	odds ratio
PD	pharmacodynamics
PET	positron emission tomography
PFS	Piper Fatigue Scale
PK	pharmacokinetics
PGA	Patient Global Assessment
PLMS	periodic leg movements during the sleep period
PP	per protocol
QoL	quality of life
RLS	Restless Legs Syndrome
SD	standard deviation
SE	standard error
SMC	standard medical care
TEAE	treatment-emergent adverse events
tid	*ter in die* (thrice daily)
TKA	total knee arthroplasty
TSAT	transferrin saturation
VO_2	oxygen consumption

Ferric carboxymaltose in patients with heart failure and iron deficiency (FAIR-HF)

SD Anker, J Comin Colet, G Filippatos, R Willenheimer, K Dickstein, H Drexler, TF Lüscher, B Bart, W Banasiak, J Niegowska, B-A Kirwan, C Mori, B v Eisenhart Rothe, SJ Pocock, PA Poole-Wilson, P Ponikowski, for the FAIR-HF Trial Investigators
N Engl J Med 2009; 361: 2436–2448. doi: 10.1056/NEJMoa0908355.
ClinicalTrials.gov number: NCT00520780

DESIGN

Randomised, double-blind, placebo-controlled, phase III study (Sponsor: Vifor Pharma)

Patients (N = 459 randomised) with

- CHF (NYHA class II or III), reduced LVEF (≤ 40% [NYHA class II] or ≤ 45% [NYHA class III])
- ID (ferritin level < 100 ng/mL or 100 – 299 ng/mL, if TSAT was < 20%) either with or without anemia (Hb level 9,5 – 13,5 g/dL)

Randomisation 2:1 to

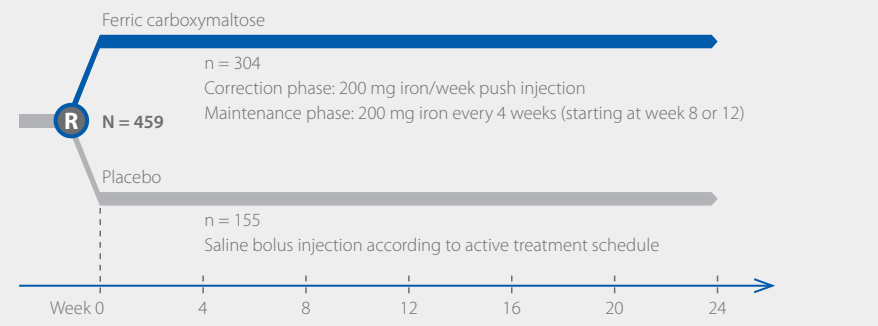
- FCM: 200 mg iron IV (n = 304)
- Placebo (n = 155)

Primary endpoints

- Self-reported Patient Global Assessment (PGA) at week 24
- NYHA functional class at week 24

Secondary endpoints

- Distance walked in 6 minutes
- Health-related QoL



RESULTS

Primary endpoints

PGA at week 24 much or moderately improved

FCM (n = 292): 50%	OR for improvement 2.51; 95% CI 1.75 – 3.61 (p < 0.001)
Placebo (n = 149): 28%	

NYHA functional class I or II at week 24

FCM (n = 294): 47%	OR for improvement by one class 2.40; 95% CI 1.55 – 3.71 (p < 0.001)
Placebo (n = 150): 30%	

Secondary endpoints

- Significant improvements with FCM in the distance on the 6-minute walk test and QoL assessments
- Similar results in ID patients with and without anemia

	Baseline	Week 4	Week 12	Week 24
6-Minute-Walk Test (mean distance, m)				
FCM	274±6	294±7*	312±6*	313±7*
Placebo	269±9	269±10	272±10	277±10
Mean study treatment effect		21±6	37±7	35±8
Health-related quality of life: EQ-5D Visual Analog Scale (mean score)				
FCM	54±1	60±1*	62±1*	63±1*
Placebo	54±1	54±2	56±2	57±2
Mean study treatment effect		6±1	6±2	7±2
Health-related quality of life: KCCQ (mean score)				
FCM	52±1	62±1*	65±1*	66±1*
Placebo	53±1	56±2	57±2	59±2
Mean study treatment effect		6±1	8±2	7±2

* p < 0.001 vs. Baseline

CONCLUSION

Treatment with IV FCM in patients with CHF and ID, with or without aneamia, improves symptoms, functional capacity, and QoL; the side-effect profile is acceptable.

Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency (CONFIRM-HF)

P Ponikowski, DJ van Veldhuisen, J Comin-Colet, G Ertl, M Komajda, V Mareev, T McDonagh,A Parkhomenko, L Tavazzi, V Levesque, C Mori, B Roubert, G Filippatos, F Ruschitzka, SD Anker, for the CONFIRM-HF Investigators
Eur Heart J 2015; 36: 657–668. doi: 10.1093/eurheartj/ehu385.
ClinicalTrials.gov number: NCT01453608

DESIGN

Randomised, double-blind, placebo-controlled, phase III, multicentre study (Sponsor: Vifor Pharma)

Patients (N = 304 randomised) with

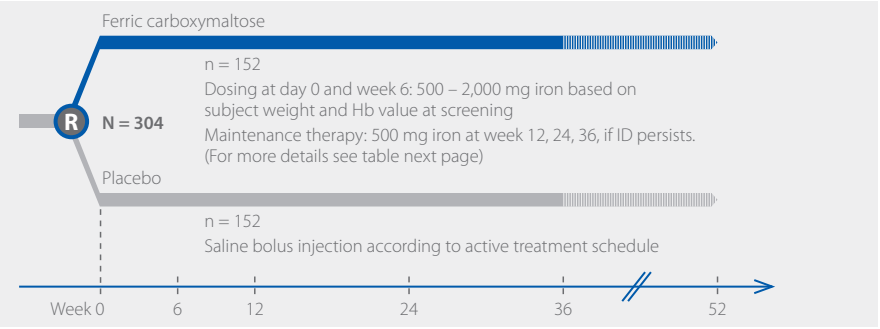
- Symptomatic HF, LVEF ≤ 45%, elevated natriuretic peptides
- ID (ferritin < 100 ng/mL or 100 – 300 ng/mL if TSAT < 20%; Hb < 15 g/dL)

Primary endpoint

- Change in 6-minutes-walk-test (6MWT) distance from baseline to week 24

Secondary endpoints (assessed at weeks 6, 12, 24, 36 and 52)

- Changes in NYHA class, 6MWT distance
- Patient Global Assessment (PGA)
- Health-related QoL, Fatigue Score
- Effect of FCM on the rate of hospitalisation for worsening HF



	Total FCM doses (mg Iron)					
	Screening Weight < 70 kg			**Screening Weight > 70 kg**		
	Screening Hb					
Hb	< 10 g/dL	10-14 g/dL	> 14 < 15 g/dL	<10 g/dL	10-14 g/dL	> 14 < 15 g/dL
Day 0	1,000 mg	1,000 mg	500 mg	1,000 mg	1,000 mg	500 mg
Week 6	500 mg	No dose	No dose	1,000 mg	500 mg	No dose
Weeks 12, 24 and 36*	If requested 500 mg	If requested 500 mg	If requested 500 mg	If requested 500 mg	If requested 500 mg	If requested 500 mg

* Dose to be administered when serum ferritin <100 ng/mL or serum ferritin 100 – 300 ng/mL with transferrin saturation < 20%

RESULTS

Number of patients

	FCM	Placebo
Full analysis set	150	151
PP analysis set	123	128

Primary endpoint

- Treatment with FCM significantly prolonged 6MWT distance at week 24 (difference FCM vs. placebo: 33 ± 11 m, p = 0.002)

Secondary endpoints

- Treatment effect of FCM was consistent in all subgroups and was sustained to week 52 (difference FCM vs. placebo: 36 ± 11 m, p < 0.001)
- Throughout the study, an improvement in NYHA class, PGA, QoL, and Fatigue Score in patients treated with FCM was detected with statistical significance observed from week 24 onwards
- Treatment with FCM was associated with a significant reduction in the risk of hospitalisations for worsening HF (HR [95% CI]: 0.39 [0.19 – 0.82], p = 0.009)

	Week 6	Week 12	Week 24	Week 36	Week 52
6-Minute-Walk Test [change from Baseline, LSM (95%CI)]					
FCM	14 (0 , 28)	15 (1, 29)	19(5, 34)*	20 (5, 34)*	14 (-1, 29)*
Placebo	1 (-13, 14)	-1 (-15, 12)	-14 (-28, 1)	-22 (-37, -8)	-22 (-37, -7)
FCM vs. Placebo	14 (-5, 33)	16 (-3, 35)	33 (13, 53)	42 (2, 62)	36 (16, 57)
Fatigue [change from Baseline, LSM (95%CI)]					
FCM	-0.4 (-0.6, -0.1)	-0.8(-1.1, -0.5)#	-0.8 (-1.1, -0.5)**	-1.0 (-1.3, -0.7)*	-0.7 (-1.0, -0.4)*
Placebo	-0.2 (-0.4, 0.1)	-0.3 (-0.6, -0.1)	-0.2 (-0.5, 0.1)	-0.2 (-0.5, 0.1)	-0.1 (-0.4, 0.2)
FCM vs. Placebo	-0.2 (-0.5, 0.2)	-0.5 (-0.9, -0.1)	-0.6 (-1.2, -0.2)	-0.8 (-1.2, -0.4)	-0.7 (-1.1, -0.2)
Health-related quality of life: EQ-5D Visual Analog Scale [change from Baseline, LSM (95%CI)]					
FCM	5.1 (3.0, 7.2)	5.2 (2.9, 7.3)	6.0 (3.8, 8.3)	7.6 (5.3, 10.0)**	7.0 (4.7, 9.4)
Placebo	3.5 (1.5, 5.6)	2.4 (o.2, 4.5)	3.2 (1.0, 5.5)	2.4 (0.04, 4.8)	4.4 (2.0, 6.9)
FCM vs. Placebo	1.5 (-1.4, 4.4)	2.8 (-0.2, 5.8)	2.8 (-0.3, 5.9)	5.2 (2.0, 8.5)	2.6 (-0.7, 5.9)
Health-related quality of life: EQ-5D Visual Analog Scale [change from Baseline, LSM (95%CI)]					
FCM	5.1 (3.0, 7.2)	5.2 (2.9, 7.3)	6.0 (3.8, 8.3)	7.6 (5.3, 10.0)**	7.0 (4.7, 9.4)
Placebo	3.5 (1.5, 5.6)	2.4 (o.2, 4.5)	3.2 (1.0, 5.5)	2.4 (0.04, 4.8)	4.4 (2.0, 6.9)
FCM vs. Placebo	1.5 (-1.4, 4.4)	2.8 (-0.2, 5.8)	2.8 (-0.3, 5.9)	5.2 (2.0, 8.5)	2.6 (-0.7, 5.9)

* p < 0.001 vs. Placebo ** p < 0.002 vs. Placebo # p < 0.009 vs. Placebo

CONCLUSION

Treatment of symptomatic, iron-deficient HF patients with FCM over a 1-year period resulted in sustainable improvement in functional capacity, symptoms, and QoL and may be associated with risk reduction of hospitalisation for worsening HF.

Effect of ferric carboxymaltose on exercise capacity in patients with chronic heart failure and iron deficiency

DJ van Veldhuisen, P Ponikowski, P van der Meer, M Metra, M Böhm, A Doletsky, AA Voors, IC Macdougall, SD Anker, B Roubert, L Zakin, A Cohen-Solal, on Behalf of the EFFECT-HF Investigators
Circulation 2017; 136: 1374–1383. doi: 10.1161/CIRCULATIONAHA.117.027497
ClinicalTrials.gov number: NCT01394562

DESIGN

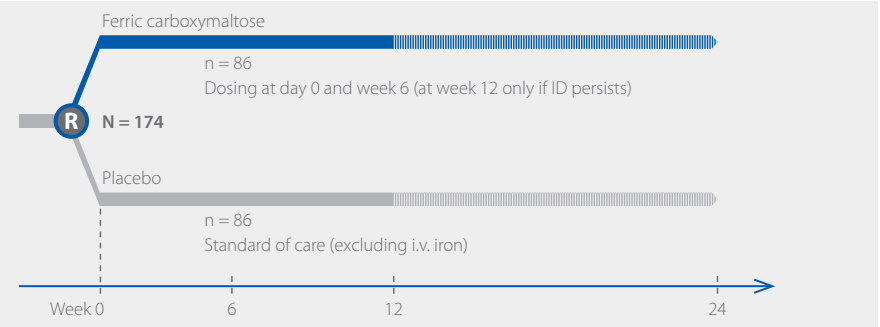
Randomised, open-label, assessor/endpoint-blinded, standard of care-controlled, phase III, multicentre trial. Safety analyses were performed on all subjects who received ≥ 1 dose of study drug or were randomized to the usual care group. (Sponsor: Vifor Pharma)

Patients (N = 174 randomised) with

- NYHA class II/III, LVEF ≤ 45%, reproducible peak VO_2 10 – 20 mL/kg/min, BNP > 100 pg/mL and/or NT-proBNP > 400 pg/mL
- Iron deficiency: serum ferritin < 100 ng/mL or 100 – 300 ng/mL if TSAT < 20%
- Hb ≤ 15 g/dL

Primary endpoint

- Change in weight-adjusted peak VO_2 from baseline to week 24



RESULTS

Number of patients

	Total	FCM	SoC
Full analysis set (FAS)	172	86	86
PP analysis set*	146	70	76
Primary endpoint analysis	121	55	66

* population consisted of all subjects who, in addition to the FAS criteria, had no major protocol violations

Primary endpoint

- Peak VO_2 decreased in control group but was maintained in patients who received FCM
- Change in Δ peak VO_2 for FCM vs. change in Δ peak VO_2 for SoC (FAS-Set): LSM ± SE difference of 1.04 ± 0.44 mL/kg/min (p = 0.02)

Secondary endpoint

Iron-related parameters: change from baseline to week 24 (FAS)

	FCM		**SMC****	
Parameter	Baseline	Week 24	Baseline	Week 24
Ferritin ng/mL, median	48	283 (150)*	53	79
TSAT %, median	17.3	27 (8)*	18.1	20.2
Hb g/dL*	12.9 (1.3)	13.9 (1.3)	13.0 (1.5)	13.2 (1.4)

* mean (standard deviation) ** 29 patients in SMC received oral iron

SAFETY

- FCM was generally well tolerated. No hypersensitivity reactions to the drug occurred, and no cases of hypophosphatemia were reported

CONCLUSION

Treatment with i.v. FCM in patients with HF and iron deficiency improves iron stores. The effect on peak VO_2, observed upon i.v. iron-treatment was favorable, compared with SoC. Whether FCM is associated with improved outcome in high-risk patients needs to be addressed in further studies.

Pharmacodynamics and safety of ferric carboxymaltose: a multiple-dose study in patients with iron-deficiency anemia secondary to a gastrointestinal disorder

P Geisser, V Rumyantsev
Arzneimittelforschung 2010; 60: 373–385

DESIGN

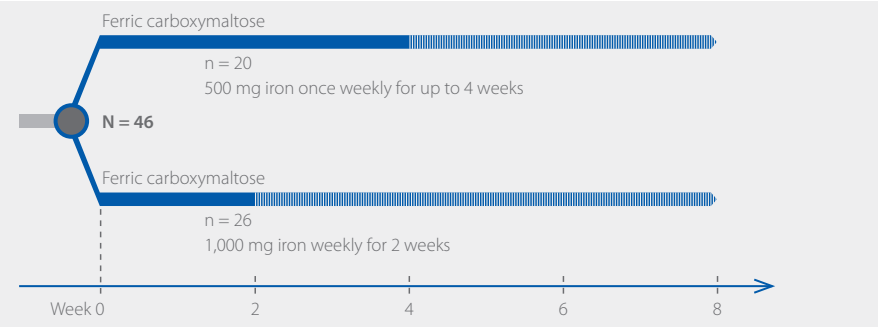
Multiple-dose, phase I/II trial (Sponsor: Vifor Pharma)

Patients (N = 46 enrolled)

Adults with moderate to severe, stable IDA (Hb level ≤ 11.0 g/dL, serum ferritin level < 100 ng/ml, and TSAT < 16%) due to gastrointestinal disorder (e.g. IBD). Total requirement of ≥ 1,000 mg iron

Objective

To evaluate the safety and tolerability and to provide data on the therapeutic benefit of FCM



RESULTS

- Clinically meaningful increase in Hb levels (≥ 1.0 g/dL) during the study in more than 97% of patients

	Cohort 1	Cohort 2
Mean cumulative iron dose	1,800 mg	1,563 mg
Patients with Hb increase of ≥ 2.0 g/dL by week 4	15/20 (75%)	19/26 (73.1%)
Mean increase in Hb (g/dL)	3.2	3.3
Patients with normal Hb levels by day 28	3/6 (50%)	(data not available)
Patients with normal Hb levels at 4-week post-treatment follow-up visit	7/19 (37%)	12/25 (48%)

- Serum ferritin levels increased rapidly at start of treatment and remained in the reference range throughout the study; increases were greater in Cohort 2
- Mean baseline TSAT values were similar in both cohorts (Cohort 1: 24.2%, Cohort 2: 20.7%), and were within the reference range at the week 4 follow-up visit (41.0% and 39.1%, respectively
- The incidence of AEs occurring after the first administration of FCM (treatment-emergent AEs, TEAE) was generally low
- There were no AEs of severe intensity, serious AEs, or deaths

CONCLUSION

The increase in serum ferritin and TSAT at the 4-week follow-up visit is indicative of a repletion of the iron stores. The results suggest that doses up to 1,000 mg IV iron administered as FCM over 15 min are well tolerated and effective in the treatment of patients with IDA due to a gastrointestinal disorder.

A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT®) randomised controlled trial

S Kulnigg, S Stoinov, V Simanenkov, LV Dudar, W Karnafel , LC Garcia, AM Sambuelli, G D'Haens, C Gasche
Am J Gastroenterol 2008; 103: 1182–1192. doi: 10.1111/j.1572-0241.2007.01744.x

DESIGN

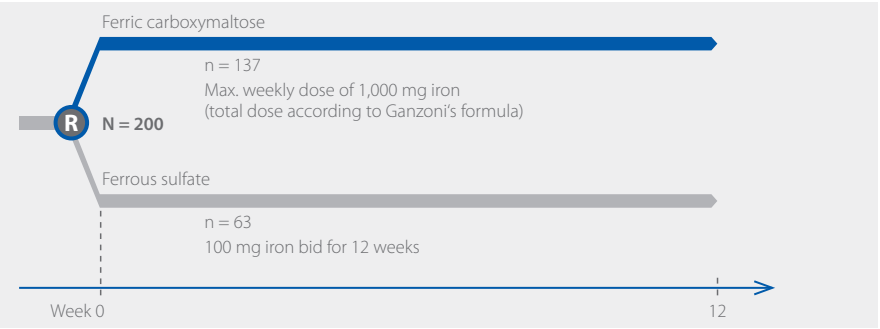
Randomised, open-label, controlled, phase III, multicentre trial (Sponsor: Vifor Pharma)

Patients (N = 200 randomised)

with IBD and IDA (Hb ≤ 10 g/dL and TSAT < 20%, or serum ferritin < 100 ng/mL)

Primary endpoint

Change in Hb from baseline to week 12



RESULTS

Number of patients (ITT set)

- FCM: n = 136
- FS: n = 60

Main results (ITT set)

- Median Hb improved with
  - FCM: from 8.7 to 12.3 g/dL
  - FS: from 9.1 to 12.1 g/dL

  demonstrating non-inferiority (p = 0.6967)
- Response (defined as Hb increase of > 2.0 g/dL) was higher for FCM at week 2 (p = 0.0051) and week 4 (p = 0.0346)
- Median ferritin increased with
  - FCM: from 5.0 to 323.5 ng/mL at week 2, followed by a continuous decrease (43.5 ng/L at week 12)
  - FS: moderately from 6.5 to 28.5 ng/mL at week 12

CONCLUSION

FCM is effective and well tolerated in IBD-associated anemia. It is noninferior to FS in terms of Hb change over 12 weeks, and provides a fast Hb increase and a sufficient refill of iron stores.

FERGIcor, a randomised controlled trial on ferric carboxymaltose for iron deficiency anemia in inflammatory bowel disease

R Evstatiev, P Marteau, T Iqbal, IL Khalif, J Stein, B Bokemeyer, IV Chopey, FS Gutzwiller, L Riopel, C Gasche; FERGI Study Group
Gastroenterology 2011; 141(3): 846-853.e1-2. doi:10.1053/j.gastro.2011.06.005.
ClinicalTrials.gov number: NCT00810030

DESIGN

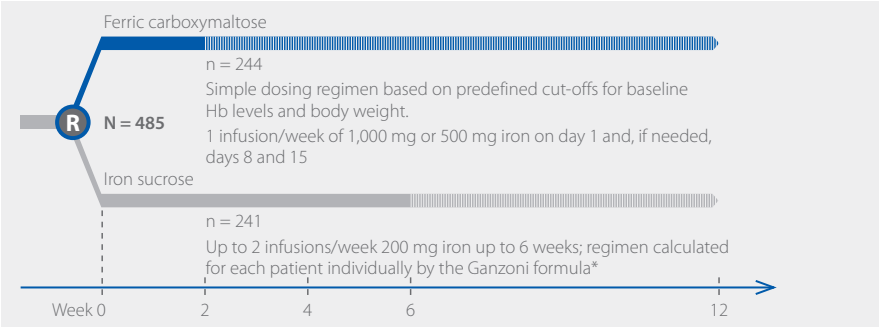
Randomised, open-label, controlled, phase III, multicentre trial (Sponsor: Vifor Pharma)

Patients (N = 485 randomised)

with mild to moderate or quiescent IBD and IDA (Hb 7–12 g/dL [female] or 7 – 13 g/dL [male] and ferritin < 100 ng/mL)

Primary endpoint

Hb response (increase of ≥ 2.0 g/dL) at week 12



* Ganzoni formula: total iron dose = [body weight x (target Hb – actual Hb)] x 2.4 + iron storage depot

RESULTS

- More patients with FCM than IS achieved Hb response or Hb normalisation:

	FCM (n = 240)	IS (n = 235)	Difference (p value)
Hb response	150 (65.8%)	118 (53.6%)	12.2% (p = 0.004)
Hb normalisation	166 (72.8%)	136 (61.8%)	11.0% (p = 0.015)

- The FCM group showed significantly stronger increases in Hb (from week 2 onward) and iron parameters (at all timepoints) compared with the IS group
- Both treatments improved QoL scores by week 12
- Deviations from scheduled total iron dosages were more frequent in the IS group

CONCLUSION

The simpler FCM-based dosing regimen showed better efficacy and compliance, as well as a good safety profile, compared with the Ganzoni-calculated IS dose regimen.

Ferric carboxymaltose prevents recurrence of anemia in patients with inflammatory bowel disease (FERGImain)

R Evstatiev, O Alexeeva, B Bokemeyer, I Chopey, M Felder, M Gudehus, T Iqbal, I Khalif, P Marteau, J Stein, C Gasche, and the FERGI Study Group
Clin Gastroenterol Hepatol 2013; 11: 269–727. doi: 10.1016/j.cgh.2012.10.013.
ClinicalTrials.gov number: NCT00810004

DESIGN

Randomised, single-blinded, placebo-controlled, phase III trial (Sponsor: Vifor Pharma)

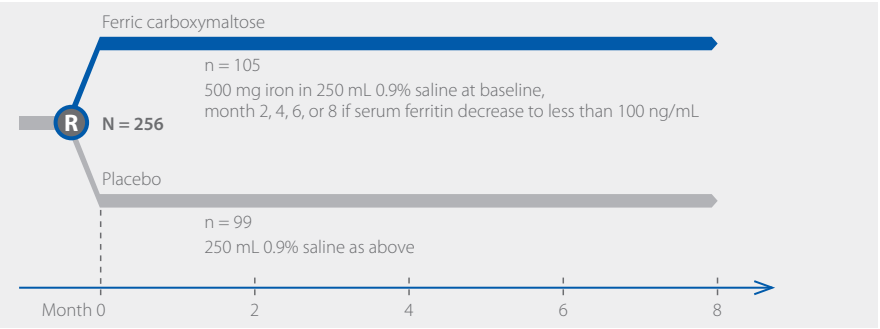
Patients (N = 256 randomised)

Nonanaemic patients with IBD and low levels of serum ferritin who had completed the FERGIcor study

Serum ferritin levels were assessed every second month to determine if administration of FCM prevents anemia

Primary endpoint

Time to recurrence of anemia within 8 months



RESULTS

Number of patients (FAS)

- FCM: n = 105
- Placebo: n = 99

Main results (FAS)

- Primary endpoint: time to anemia recurrence was longer in the FCM group (HR 0.62; 95% CI 0.38 –1.00; p = 0.049)
- Anemia recurred in 26.7% of subjects given FCM and in 39.4% given placebo (FAS)
- Markers of body levels of iron increased or remained at normal levels in subjects given FCM (ferritin increased by 30.3 ng/mL, TSAT increased by 0.6%) but decreased in the group given placebo (ferritin decreased by 36.1 ng/mL, TSAT decreased by 4.0%)
- Changes in QoL and disease activity were comparable between groups

CONCLUSION

FCM treatment prevents recurrence of anemia in patients with IBD, compared with placebo. Nevertheless, the high rate of anemia recurrence warrants optimization of the frequency and requirements for FCM treatment.

Iron deficiency generates secondary thrombocytosis and platelet activation in IBD: the randomised, controlled thromboVIT trial

S Kulnigg-Dabsch, W Schmid, S Howaldt, J Stein, O Mickisch, T Waldhör, R Evstatiev, H Kamali, I Volf, and C Gasche
Inflamm Bowel Dis 2013; 19: 1609–1616. doi: 10.1097/MIB.0b013e318281f4db
ClinicalTrials.gov number: NCT00882414

DESIGN

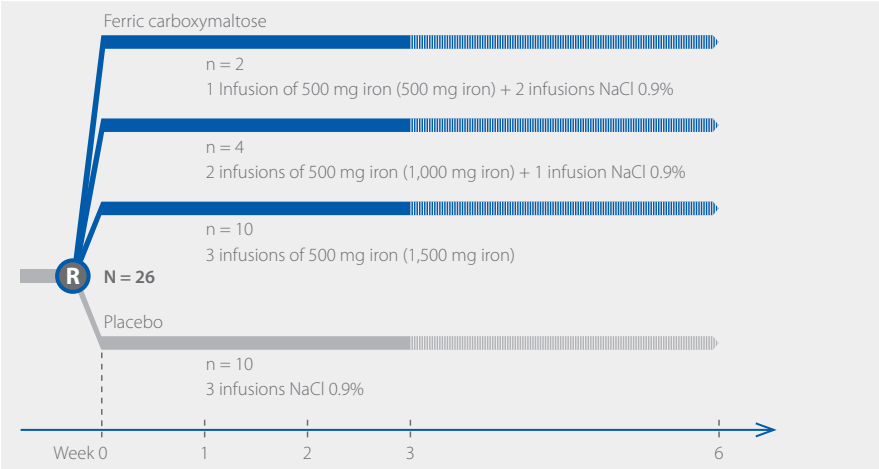
Randomised single-blinded, placebo-controlled, phase II, multicentre trial
(Sponsor: Vifor Pharma)

Patients (N = 26 randomised)

with IBD and secondary thrombocytosis (platelets > 450 G/L)

Primary endpoint

Decrease of platelet counts of ≥ 25% after 6 weeks



RESULTS

	FCM	Placebo	p value
ITT set	n = 16	n = 9	
PP set	n = 8	n = 7	
Primary endpoint: drop in platelets > 25% (PP set)	4/8 (50%)	1/7 (14%)	0.143
Drop of mean platelet counts (ITT set)	536 – 411 G/L	580 – 559 G/L	0.002

- Disease activity and megakaryopoietic growth factors remained unchanged
- Hb and iron parameters increased on FCM

CONCLUSION

FCM lowers platelet counts and platelet activation in patients with IBD-associated secondary thrombocytosis.

The safety and efficacy of intravenous ferric carboxy-maltose in anaemic patients undergoing haemodialysis: a multicentre, open-label, clinical study

A Covic, G Mircescu
Nephrol Dial Transplant 2010; 25(8): 2722–2730. doi: 10.1093/ndt/gfq069

DESIGN

Open-label, single-arm, phase II, multicentre study (Sponsor: Vifor Pharma)

Patients: (N = 163 enrolled)

with IDA (Hb ≤ 11.0 g/dL and either serum ferritin ≤ 200 ng/mL or TSAT < 20%) undergoing haemodialysis (HD)

Objective

To assess the safety and efficacy of multiple doses of IV iron as FCM, given as single, bolus-push injections

Treatment

100 – 200 mg of iron as FCM via an IV bolus-push injection into the HD venous line, 2 to 3 times weekly for ≤ 6 weeks

RESULTS

150/163 (92%) patients completed the study

Mean ± SD total cumulative dose of iron as FCM administered was 2,133.3 ± 57.7 mg iron

Overall, 100 out of 162 (61.7%; ITT population) patients were treatment responders (i.e. patients attaining ≥ 1.0 g/dL increase in Hb from baseline at any time during the study)

Mean Hb levels increased from 9.1 ± 1.30 g/dL at baseline to 10.3 ± 1.63 g/dL at follow-up

CONCLUSION

FCM is well-tolerated and effective in the correction of Hb levels and iron stores in patients with IDA undergoing HD. The clinically relevant increase in Hb in the majority of patients can be solely attributed to efficient iron utilisation.

A randomised controlled trial comparing intravenous ferric carboxymaltose with oral iron for treatment of iron deficiency anemia of non-dialysis-dependent chronic kidney disease patients

WY Qunibi, C Martinez, M Smith, J Benjamin, A Mangione, SD Roger
Nephrol Dial Transplant 2011; 26: 1599–1607. doi: 10.1093/ndt/gfq613

DESIGN

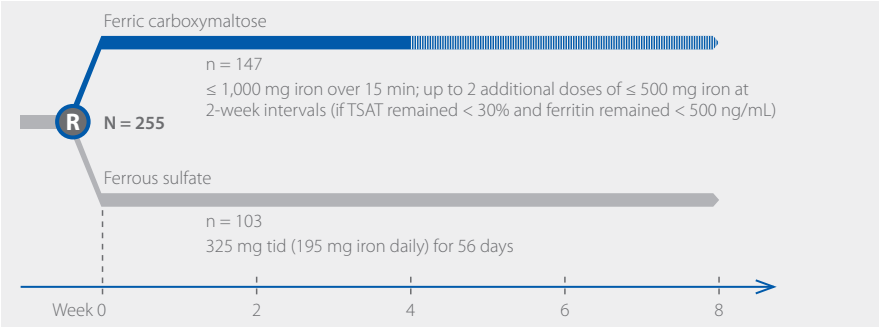
Randomised, open-label, controlled, phase III, multicentre study
(Sponsor: Luitpold Pharmaceuticals)

Patients (N = 255 randomised)

with non-dialysis-dependent CKD (NDD-CKD) (GFR ≤ 45 mL/min/1.73 m^2, Hb ≤ 11 g/dL, TSAT ≤ 25%, ferritin ≤ 300 ng/mL)

Primary efficacy end point

- Percentage of subjects achieving an increase in Hb of ≥1.0 g/dL at any study point between baseline and End of Study or
- Introduction or dose increase of ESA, blood transfusion, or use of iron outside of protocol



RESULTS

	FCM	FS	p value
Number of patients (modified ITT population)	144	101	
Subjects achieving a Hb increase ≥ 1 g/dL at any time	60.4%	34.7%	< 0.001
Mean increase in Hb at day 42	0.95 ± 1.12 g/dL	0.50 ± 1.23 g/dL	0.005
Mean increase in ferritin at day 42	432 ± 189 ng/mL	18 ± 45 ng/mL	< 0.001
Mean increase in TSAT at day 42	13.6 ± 11.9%	6.1 ± 8.1%	< 0.001

CONCLUSIONS

1,000 mg of iron as FCM can be rapidly administered, is more effective and is better tolerated than oral iron for treatment of iron deficiency in NDD-CKD patients.

Intravenous ferric carboxymaltose versus standard medical care in the treatment of iron deficiency anemia in patients with chronic kidney disease: a randomised, active-controlled, multicentre study

C Charytan, MV Bernardo, TA Koch, A Butcher, D Morris, DB Bregman
Nephrol Dial Transplant 2013; 28: 953–964. doi: 10.1093/ndt/gfs528.
ClinicalTrials.gov number: NCT00548691

DESIGN

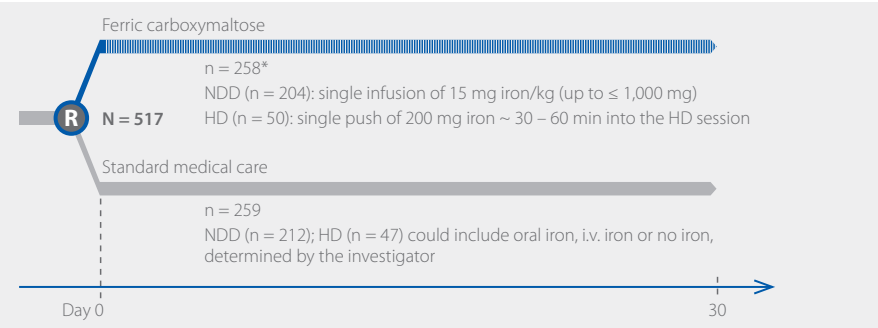
Randomised, open-label, controlled, phase III, multicentre study
(Sponsor: Luitpold Pharmaceuticals)

Patients (N = 517 randomised)

with CKD (HD or NDD) and IDA (NDD-CKD subjects: Hb ≤ 11.5 g/dL, TSAT ≤ 30% and serum ferritin ≤ 300 ng/mL; HD-CKD subjects: Hb ≤ 12.5 g/dL, TSAT ≤ 30% and serum ferritin ≤ 500 ng/mL)

Objective

To evaluate the safety of the maximum administered dose FCM compared with standard medical care (SMC)



* 4 subjects did not receive study medication

RESULTS

Number of patients (modified ITT population)

- n = 249 in both groups

Main efficacy results

- No statistically significant differences between the FCM and SMC groups in indices of Hb improvement, including proportions of patients achieving a ≥ 1 g/dL increase in Hb and proportions of patients achieving Hb level of > 12 g/dL

CONCLUSION

FCM in doses of 200 mg for HD-CKD patients and up to 1,000 mg in NDD-CKD patients were well tolerated and displayed comparable efficacy to other IV iron formulations.

Ferric carboxymaltose in patients with iron-deficiency anemia and impaired renal function: the REPAIR-IDA trial

JE Onken, DB Bregman, RA Harrington, D Morris, J Buerkert, D Hamerski, H Iftikhar, R Mangoo-Karim, ER Martin, CO Martinez, GE Newman, WY Qunibi, DL Ross, B Singh, MT Smith, A Butcher, TA Koch, LT Goodnough
Nephrol Dial Transplant 2014; 29: 833–842. doi: 10.1093/ndt/gft251.
ClinicalTrials.gov number: NCT 00981045

DESIGN

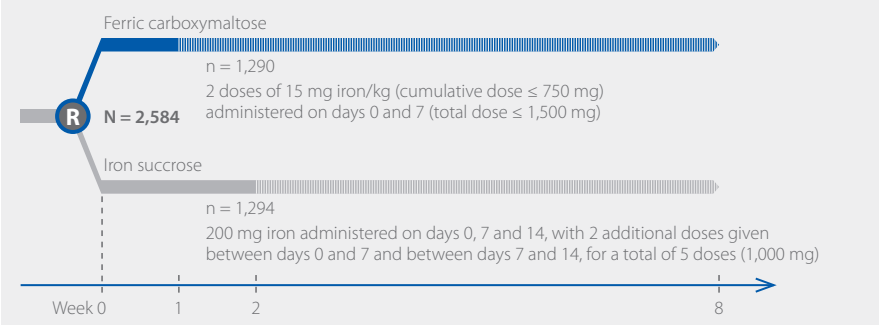
Randomised, open-label, active-controlled, phase III, multicentre, non-inferiority trial (Sponsor: Luitpold Pharmaceuticals)

Patients (N = 2,584 randomised)

with NDD-CKD and IDA (Hb ≤ 11.5 g/dL, serum ferritin ≤ 100 ng/mL, or serum ferritin ≤ 300 ng/mL when TSAT was ≤ 30%)

Primary efficacy endpoint

Mean change from baseline Hb to highest observed Hb at any time between baseline and the end of treatment period (day 56) or the time of intervention



RESULTS

Number of patients (modified ITT population)

- FCM: n = 1,249
- IS: n = 1,244

Main efficacy results (modified ITT population)

- Mean Hb increase was 1.13 g/dL in the FCM group and 0.92 g/dL in the IS group (95% CI 0.13 – 0.28)
- Similar results were observed across all subgroups except stage 2 CKD
- More subjects in the FCM group achieved a Hb increase of ≥ 1.0 g/dL between baseline and day 56 (48.6 vs. 41.0%; 95% CI 3.6 – 11.6%)

CONCLUSION

Two 750-mg infusions of FCM are a well tolerated and an effective alternative to multiple lower dose IS infusions in NDD-CKD patients with IDA.

FIND-CKD: a randomised trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anemia

IC Macdougall, AH Bock, F Carrera, K-U Eckardt, C Gaillard, D VanWyck, B Roubert, JG Nolen, SD Roger
on behalf of the FIND-CKD Study Investigators
Nephrol Dial Transplant 2014; 29: 2075–2084. doi: 10.1093/ndt/gfu201.
ClinicalTrials.gov number: NCT 00994318

DESIGN

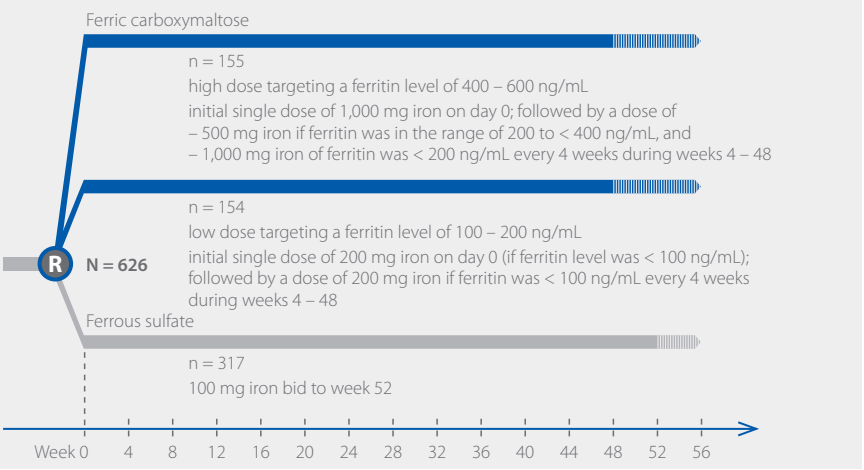
Prospective, randomised, open-label, three-arm, phase IIIb, multicentre study
(Sponsor: Vifor Pharma)

Patients (N = 626)

with NDD-CKD and IDA (at least one Hb level between 9 and 11 g/dL, any serum ferritin level < 100 or < 200 ng/mL with TSAT < 20%, within 4 weeks of randomisation)

Primary endpoint

Time to initiation of other anemia management (ESA, other iron therapy or blood transfusion) or Hb trigger of two consecutive values < 10 g/dL during weeks 8 – 52



RESULTS

Main efficacy results (ITT population)

	High-ferritin FCM (n = 153)	Low-ferritin FCM (n = 152)	FS (n = 308)	Difference
Time to initiation of other anemia management or Hb trigger (primary endpoint)	36 (23.5%)	49 (32.2%)	98 (31.8%)	HR: 0.65; 95% CI 0.44 – 0.95; p = 0.026 (high-ferritin FCM vs. FS)
Increase in Hb (from baseline to month 12), LSM (SE)	1.4 (0.1) g/dL	0.9 (0.1) g/dL	1.0 (0.1) g/dL	p = 0.014 (high-ferritin FCM vs. FS)
Proportion of patients with Hb increase ≥ 1 g/dL	87 (56.9%)	52 (34.2%)	99 (32.1%)	HR: 2.04; 95% CI 1.52 – 2.72; p < 0.001 (high-ferritin FCM vs. FS)

LS: least squares means; SD: standard deviation

- FCM targeting a ferritin of 400 – 600 ng/mL is more effective than oral iron in reducing or delaying the need for additional or alternative anemia management

CONCLUSION

Compared with oral iron, IV FCM targeting a ferritin of 400 – 600 ng/mL quickly reached and maintained Hb level, and delayed and/or reduced the need for other anemia management including ESAs.

Post-Hoc Analysis of FIND-CKD trial

Erythropoietic response to oral iron in patients with nondialysis-dependent chronic kidney disease in the FIND-CKD trial

IC Macdougall, AH Bock, F Carrera, KU Eckardt, C Gaillard, D Van Wyck, Y Meier, S Larroque, A Perrin, SD Roger
on behalf of the FIND-CKD Study Investigators
Clinical Nephrology 2017; 88(12): 301-310. doi: 10.5414/CN109198
Clinicaltrials.gov number: NCT00994318

DESIGN

FIND-CKD was a 1-year, randomized, multicenter trial of iron therapy in patients with non-dialysis-dependent chronic kidney disease (ND-CKD), anemia, and iron deficiency, without erythropoiesis-stimulating agent (ESA) therapy.

A post hoc analysis of FIND-CKD was performed to evaluate erythropoietic response rates defined as ≥ 1 g/dL increase in hemoglobin (Hb) from baseline, before initiation of alternative anemia therapy (i.e., ESA, transfusion, or intravenous iron).
(Sponsor: Vifor Pharma)

Patients (N = 613 randomised)

The study population comprised adult patients with ND-CKD. Key eligibility criteria were ≥ 1 Hb level between 9 and 11 g/dL, with any ferritin level < 100 µg/L (or < 200 µg/L with transferrin saturation (TSAT) < 20%), within 4 weeks of randomization, and estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73m^2. No ESA was to have been given in the 4 months prior to randomization. Patients with a documented history of discontinuing oral iron therapy due to significant gastrointestinal distress, or who had known active infection, C-reactive protein (CRP) > 20 mg/L or overt bleeding were excluded, as were patients with active malignancy.

Objective of post-hoc analysis:

To evaluate erythropoietic response rates to oral iron over time in iron-deficient anemic patients with ND-CKD. In this post-hoc analysis, response rates were defined as ≥ 1 g/dL increase in Hb vs. baseline.

RESULTS

Number of patients

- Ferric carboxymaltose (FCM) high-ferritin: n = 153 (ITT population)
- FCM low-ferritin: n = 152 (ITT population)
- Oral iron: n = 308 (ITT population). Among the 308 patients, Hb levels were available at baseline and at week 4 in 292 patients

Main response rate results

- 63/292 (21.6%) of patients without alternative anemia therapy showed a response at week 4
- Among the 229 nonresponders at week 4 with oral iron therapy, 48.8% showed a cumulative response on ≥ 1 occasion by week 52 (11.1%, 19.9%, 25.9%, and 28.7% had a response at weeks 8, 12, 24, and 52, respectively), and 27.9% had received alternative iron therapy by week 52 (see Table 1)
- The response rates at week 4 in the high-ferritin and low-ferritin FCM groups were 40.9% (61/149) and 13.9% (20/144), respectively

- Baseline levels of Hb, ferritin, and transferrin saturation were lower in responders than in nonresponders, independently of their study arm
- Neither concomitant medication nor adherence (as assessed by medication count) was substantially different between early responders and nonresponders

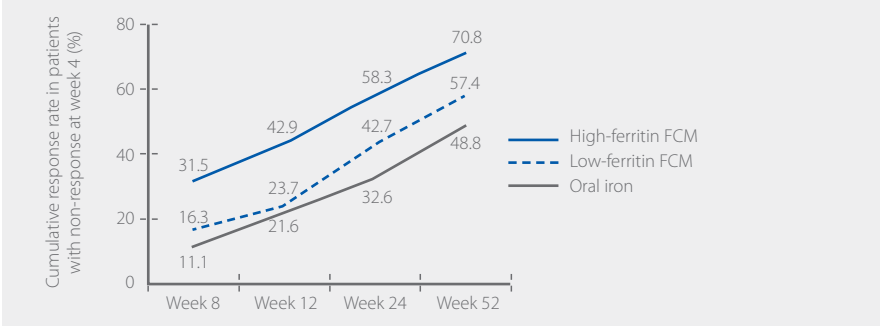


Figure 1: Cumulative response to iron therapy by weeks 8, 12, 24 and 52 in patients who were non-responders at week 4.

CONCLUSION

Four weeks after starting oral iron therapy, only 21.6% of anemic patients with ND-CKD and iron deficiency showed an Hb increase of at least 1 g/dL.

The strikingly higher rates of response in the high-ferritin FCM group highlight the potential benefit of switching oral iron nonresponders to IV iron therapy. Earlier consideration of alternative therapy could improve anemia management in this population.

Post-Hoc Analysis of FIND-CKD trial

Safety of intravenous ferric carboxymaltose versus oral iron in patients with nondialysis-dependent CKD: an analysis of the 1-year FIND-CKD trial

SD Roger, CA Gaillard, AH Bock, F Carrera, KU Eckardt, DB Van Wyck, M Cronin, Y Meier, S Larroque, IC Macdougall
Nephrol Dial Transplant 2017; 32(9): 1530-1539. doi: 10.1093/ndt/gfw264
Clinicaltrials.gov number: NCT00994318

DESIGN

FIND-CKD was an open-label, multicenter, prospective, randomised three-arm study of IV ferric carboxymaltose (FCM) versus oral iron in patients with nondialysis-dependent chronic kidney disease (CKD) and iron deficiency anemia who were not receiving treatment with an erythropoiesis-stimulating agent (ESA).

A post hoc analysis of FIND-CKD was performed to evaluate adverse event rates per 100 patient-years to assess the safety of FCM versus oral iron. (Sponsor: Vifor Pharma)

Patients (N = 616 randomised)

Adult patients with nondialysis-dependent CKD were eligible if (i) at least one Hb level was 9–11 g/dL; (ii) any ferritin level was < 100 µg/L, or < 200 µg/L with TSAT < 20%; (iii) estimated glomerular filtration rate (eGFR) was ≤ 60 mL/min/1.73 m^2 and eGFR loss was ≤ 12 mL/min/1.73 m^2/year with predicted eGFR at 12 months ≤ 15 mL/min/1.73 m^2; and (iv) no ESA therapy was received within 4 months of randomization.

Primary endpoint

The primary objective of the study was to test whether FCM reduces the need for alternative anemia therapy (e.g. blood transfusion or ESA therapy) compared with oral iron in this setting. Safety data were captured throughout the 1-year study.

Objective

A post hoc analysis of adverse event rates per 100 patient-years was performed to assess the safety of FCM versus oral iron over an extended period.

RESULTS

Number of patients

- FCM high-ferritin: n = 154 (received allocated intervention, safety population), n = 132 (completed follow-up)
- FCM low-ferritin: n = 150 (received allocated intervention, safety population), n = 132 (completed follow-up)
- Oral iron: n = 312 (received allocated intervention, safety population), n = 245 (completed follow-up)

Main efficacy results

- The mean [standard deviation (SD)] cumulative dose of FCM of the safety population was 2,685 (978) mg iron and 1,040 (618) mg iron in the high ferritin and low ferritin groups, respectively. The mean (SD) cumulative dose of oral iron was 52,435 (24,768) mg iron, and the mean (SD) total number of oral iron tablets was 524 (248) (range 2 – 800)
- The incidence of one or more adverse events was 91.0, 100.0 and 105.0 per 100 patient-years in the high ferritin FCM, low ferritin FCM and oral iron groups, respectively (see Table 1)
- The incidence of adverse events with a suspected relation to study drug was 15.9, 17.8 and 36.7 per 100 patient-years in the three groups

- The most common adverse events were gastrointestinal, the incidence of which was 23.1, 29.5 and 52.7 per 100 patient-years in the high ferritin FCM, low ferritin FCM and oral iron groups, respectively
- For serious adverse events, the incidence was 28.2, 27.9 and 24.3 per 100 patient-years. The incidence of cardiac disorders and infections was similar between groups
- The incidences of adverse events and serious adverse events in patients with serum ferritin ≥ 800 µg/L (80.5 and 24.4%) were comparable to those seen in the overall safety population
- No patient with ferritin ≥ 800 µg/L discontinued the study drug due to adverse events
- Estimated glomerular filtration rate remained stable in all groups

Table 1: Excerpt of the incidences of one or more adverse event per 100 patient years during the safety period[a]

	All events			Events with suspected relation to study drug		
	High ferritin FCM (n = 154)	**Low ferritin FCM (n = 150)**	**Oral Iron (n = 312)**	**High ferritin FCM (n = 154)**	**Low ferritin FCM (n = 150)**	**Oral Iron (n = 312)**
Adverse events (AE) /100 patient years	**91.0**	**100.0**	**105.0**	**15.9**	**17.8**	**36.7**
No. of patients with any AE (%)	126 (81.8)	129 (86.0)	255 (81.7)	22 (14.3)	23 (15.3)	89 (28.5)
Median time (days) to first event	46	57	35	148	111	29
Gastrointestinal disorders (/100 patient years)	23.1	29.5	52.7	3.6	4.7	26.8
Infections (/100 patient years)	36.8	39.5	39.1	2.9	1.6	2.9
Cardiac disorders (/ 100 patient years)	15.2	10.9	11.9	1.4	0.8	-
Serious adverse events (SAE) /100 patient years	**28.2**	**27.9**	**24.3**	**-**	**-**	**0.4**
Median time (days) to first event	143	134	67	-	-	-
Cardiac disorders (/100 patient years)	7.2	5.4	5.8	-	-	-
Infections (/100 patient years)	4.3	3.9	4.9	-	-	-

The safety population included all patients who received one or more doses of randomised treatment.

[a] The safety period included all events up to the point at which another anemia therapy was initiated and/or the randomised study medication was discontinued.

CONCLUSION

These results support the conclusion that correction of iron deficiency anemia with IV FCM is safe in patients with nondialysis-dependent CKD.

Intravenous ferric carboxymaltose compared with oral iron in the treatment of postpartum anemia

DB Van Wyck, MG Martens, MH Seid, JB Baker, Mangione
Obstet Gynecol 2007; 110: 267–278.
ClinicalTrials.gov number: NCT00396292

DESIGN

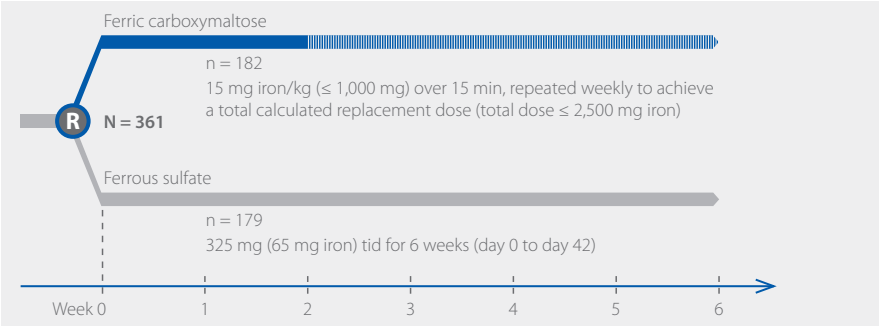
Randomised, open-label, active-controlled, phase III, multicentre, non-inferiority trial (Sponsor: Luitpold Pharmaceuticals)

Patients (N = 361 randomised)

Anaemic women within 10 days postpartum

Primary endpoint

Rise in Hb of ≥ 2.0 g/dL within 42 days after baseline



RESULTS

- 174 patients received 350 IV doses of FCM (mean total dose 1,403.1 mg) in 3, 2, or 1 injection (10.9%, 79.3%, or 9.8% of patients, respectively); 178 received FS

Main efficacy results (ITT population)

	FCM (n = 168)	FS (n = 169)	p value
Patients who achieved a Hb rise ≥ 2.0 g/dL within 42 days (primary endpoint)	96.4%	94.1%	= 0.443
Time to Hb rise ≥ 2.0 g/dL (days)	7.0	14.0	< 0.001
Patients who achieved a Hb rise ≥ 3.0 g/dL at any time	86.3%	60.4%	< 0.001
Patients who achieved a Hb ≥ 12.0 g/dL	90.5%	68.6%	< 0.001

CONCLUSION

Large-dose IV FCM administration is effective for the treatment of postpartum anemia. When compared with oral FS, IV FCM is better tolerated, prompts a more rapid Hb response, and corrects anemia more reliably.

Comparative efficacy and safety of intravenous ferric carboxymaltose in the treatment of postpartum iron deficiency anemia

C Breymann, F Gliga, C Bejenariu, N
Strizhova Int J Gynaecol Obstet 2008; 101: 67–73. doi:10.1016/j.ijgo.2007.10.009

DESIGN

Randomised, open-label, controlled, parallel-group, phase III, multicentre study (Sponsor: Vifor Pharma)

Patients (N = 349 randomised)

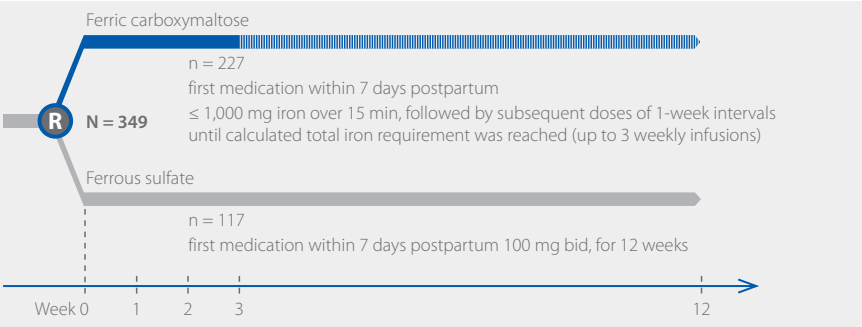
Women with postpartum IDA

Primary efficacy endpoint

Change from baseline to week 12 in Hb levels

Main safety endpoint

Treatment-emergent adverse events in the mother and breast-fed infant



RESULTS

Number of Patients (PP set)

- FCM: n = 179
- FS: n = 89

Main results

- FCM was as effective as oral FS in changing Hb, despite the much shorter treatment period (2 weeks vs. 12 weeks)
- Change from baseline in ferritin levels was significantly higher in the FCM group compared to the FS group ($p < 0.0001$)
- Iron carboxymaltose was well tolerated and treatment was not associated with any clinically relevant safety concerns

CONCLUSION

Parenteral FCM is an effective treatment option for postpartum anemia, with advantages of a shorter treatment period, better compliance, rapid normalisation of iron storages, and lower incidence of gastrointestinal side effects.

Ferric carboxymaltose injection in the treatment of postpartum iron deficiency anemia: a randomised controlled clinical trial

MH Seid, RJ Derman, JB Baker, W Banach, C Goldberg, R Rogers
Am J Obstet Gynecol 2008; 199: 435.e1–435.e7. doi: 10.1016/j.ajog.2008.07.046
ClinicalTrials.gov number: NCT00354484

DESIGN

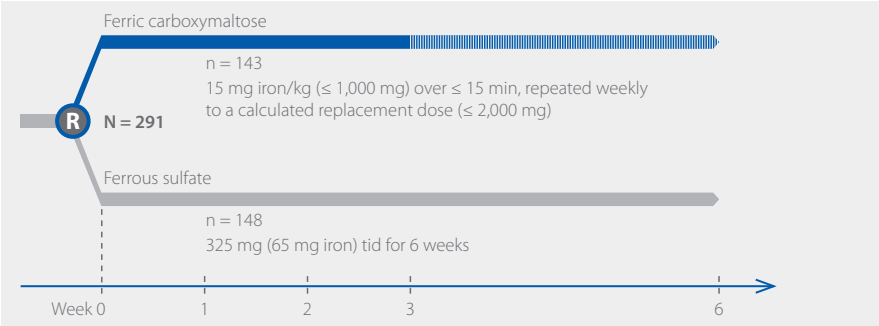
Randomised, open-label, controlled, phase III, multicentre study
(Sponsor: Luitpold Pharmaceuticals)

Patients (N = 291 randomised)

Women with postpartum anemia, less than 10 days after delivery

Primary efficacy endpoint

Percentage of subjects achieving Hb > 12 g/dL between baseline and end of study



RESULTS

Number of patients (modified ITT population)

- FCM: n = 139
- FS: n = 147

FCM-treated subjects were significantly more likely to

- achieve a Hb > 12 g/dL in a shorter time period with a sustained Hb > 12 g/dL at day 42
- achieve Hb rise ≥ 3 g/dL more quickly
- attain higher serum TSAT and ferritin levels

CONCLUSION

IV FCM was well tolerated with an efficacy superior to oral FS in the treatment of post-partum IDA.

Large-dose intravenous ferric carboxymaltose injection for iron deficiency anemia in heavy uterine bleeding: a randomised, controlled trial

DB VanWyck, A Mangione, J Morrison, P Earl Hadley, JA Jehle, and LT Goodnough for the Ferric Carboxymaltose Study Group.
Transfusion 2009; 49: 2719–2728. doi: 10.1111/j.1537-2995.2009.02327.x.
ClinicalTrials.gov number: NCT00395993

DESIGN

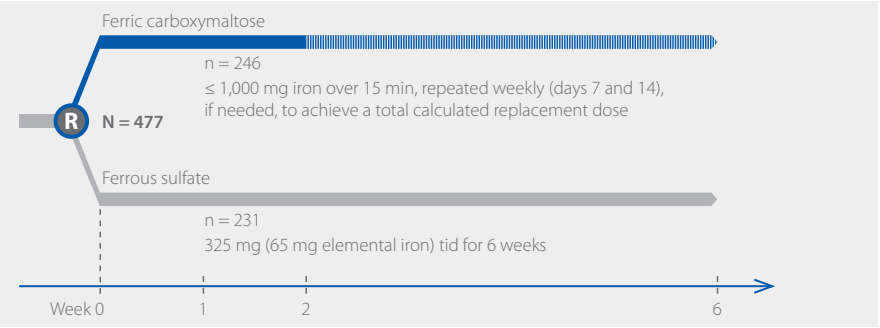
Randomised, open-label, active-controlled, phase III, multicentre trial with two parallel treatment groups (Sponsor: Luitpold Pharmaceuticals)

Patients (N = 477 randomised)

Women with IDA due to heavy uterine bleeding

Primary endpoint

Increase in Hb level of ≥ 2.0 g/dL within 42 days after baseline



RESULTS

	FCM	FS	Difference
Number of patients (ITT population)	228	225	
Patients with Hb increase of ≥ 2.0 g/dL (primary endpoint)	82%	62%	95% CI 12.2 – 28.3 p < 0.001
Patients with Hb increase of ≥ 3.0 g/dL	53%	36%	p < 0.001
Patients who achieved correction of anemia (Hb ≥ 12 g/dL)	73%	50%	p < 0.001

- Patients treated with FCM compared to those prescribed FS reported greater gains in vitality and physical function and experienced greater improvement in symptoms of fatigue ($p < 0.05$)

CONCLUSION

In patients with IDA due to heavy uterine bleeding, rapid IV administration of large doses of FCM is more effective than oral iron therapy in correcting anemia, replenishing iron stores, and improving QoL.

Evaluation of a single dose of ferric carboxymaltose in fatigued, iron-deficient women – PREFER a randomised, placebo-controlled study

B Favrat, K Balck, C Breymann, M Hedenus, T Keller, A Mezzacasa, C Gasche
PLoS ONE 2014; 9(4): e94217. doi: 10.1371/journal.pone.0094217.
ClinicalTrials.gov number: NCT01110356

DESIGN

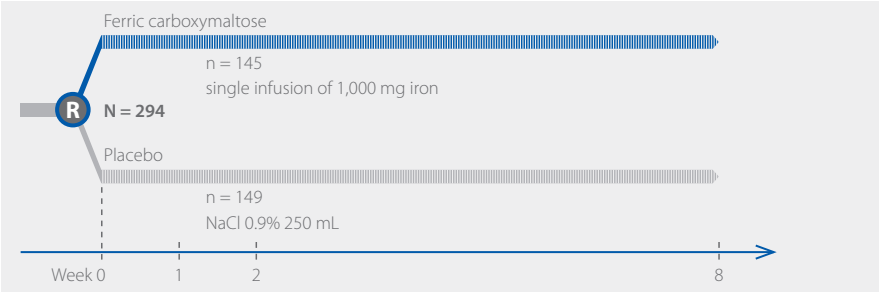
Randomised, single-blinded, placebo-controlled, phase IV, multicentre study (Sponsor: Vifor Pharma)

Patients (N = 294 randomised)

Premenopausal women with ID (ferritin < 50 ng/mL and TSAT < 20%, or ferritin < 15 ng/mL; normal or borderline Hb [≥ 115 g/L]) and symptomatic, unexplained fatigue

Primary endpoint

Proportion of patients with reduced fatigue (≥ 1 point decrease in Piper Fatigue Scale [PFS] score from baseline to day 56)



RESULTS

Number of patients (FAS/ITT population)

- FCM: n = 144
- Placebo: n = 146

Main efficacy results

- Fatigue was reduced in 65.3% (FCM) and 52.7% (placebo) of patients (OR 1.68, 95% CI 1.05 – 2.70; p = 0.03)
- A 50% reduction of PFS score was achieved in 33.3% FCM- vs. 16.4% placebo-treated patients (p < 0.001)
- At day 56, all FCM-treated patients had Hb levels ≥ 120 g/L (vs. 87% at baseline); with placebo, the proportion decreased from 86% to 81%
- Mental QoL (SF-12) and the cognitive function scores improved better with FCM
- 'Power of attention' improved better in FCM-treated patients with ferritin < 15 ng/mL

CONCLUSION

A single infusion of FCM improved fatigue, mental QoL, cognitive function and erythropoiesis in iron-deficient women with normal or borderline Hb. Although more side effects were reported compared to placebo, these side effects were mild or moderate. FCM can be an effective alternative in patients who cannot tolerate or use oral iron, the common treatment of iron deficiency.

Ferric carboxymaltose vs. oral iron in the treatment of pregnant women with iron deficiency anemia: an international, open-label, randomised controlled trial (FER-ASAP)

C Breymann, N Milman, A Mezzacasa, R Bernard, J Dudenhausen, on behalf of the FER-ASAP investigators
J Perinat Med 2017; 45(4): 443–453. doi: 10.1515/jpm-2016-0050.
ClinicalTrials.gov number: NCT01131624

DESIGN

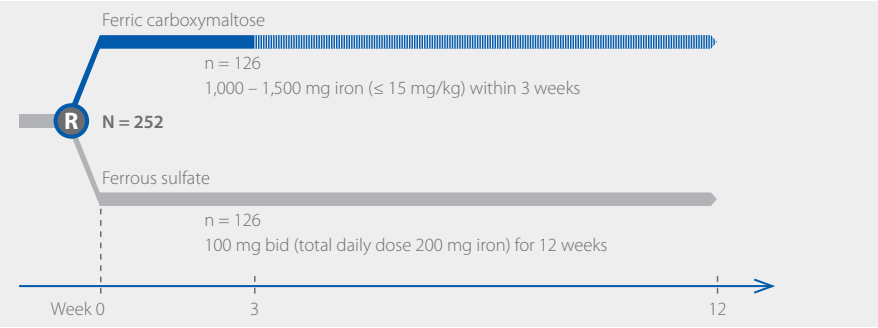
Randomised, open-label, controlled phase IIIb, multicentre study (Sponsor: Vifor Pharma)

Patients (N = 252 randomised)

Pregnant women (gestational weeks 16 – 33) with IDA (serum ferritin levels ≤ 20 ng/mL, Hb 8.0 – 10.4 g/dL for gestation weeks 16 – 26 or Hb ≤ 11.0 g/dL for gestation weeks 27–33)

Primary efficacy endpoint

Change in Hb from baseline to week 3



Secondary objectives

Safety and tolerability of FCM in pregnant women and their newborns; safety data were summarized descriptively

RESULTS

Number of patients (FAS)

- FCM: n = 121
- FS: n = 115

Main efficacy results

- Hb levels improved at comparable rates across both treatments at week 3; therefore, the primary efficacy endpoint (superiority of FCM) was not met at week 3
- Significantly more women achieved anemia correction with FCM vs. FS (Hb ≥ 11.0 g/dL; 84% vs. 70%; OR 2.06, 95% CI 1.07, 3.97; p = 0.031) and within a shorter time frame (median 3.4 vs. 4.3 weeks)
- FCM treatment significantly improved vitality (p = 0.025) and social functioning (p = 0.049) prior to delivery

Main safety results

FCM was well tolerated in pregnant women. The incidence of TEAEs was similar between the treatment arms. The safety profile was consistent with the outcome of prior studies.

CONCLUSION

During late-stage pregnancy, FCM may be a more appropriate option than first-line oral iron for rapid and effective anemia correction, with additional benefits for vitality and social functioning.

Ferric carboxymaltose as treatment in women with iron-deficiency anemia

MH Seid, AD Butcher, A Chatwani
Anemia 2017; 2017: ID 9642027. doi: 10.1155/2017/9642027
Clinicaltrials.gov number: NCT00548860

DESIGN

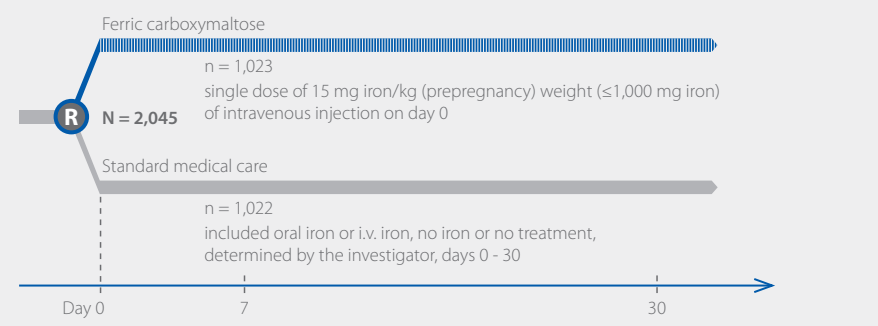
Randomised, open-label, multicenter study; collection of safety data for 30 days (Sponsor: Luitpold Pharmaceuticals)

Patients (N = 2,045 randomised)

Women with iron-deficiency anemia (IDA) (Hb ≤ 11.0 g/dL or point-of-care Hb ≤ 11.5 g/dL); postpartum women and women with heavy menstrual bleeding (HMB)

Safety and efficacy endpoints

To evaluate safety (primary endpoint defined as incidence of serious AEs) and efficacy (secondary endpoint) of intravenous ferric carboxymaltose (FCM) compared with standard medical care (SMC).



RESULTS

Number of patients

- FCM: n = 996 (received allocated intervention, safety population), n = 860 (completed follow-up)
- SMC: n = 1022 (received allocated intervention, safety population), n = 847 (completed follow-up)

Main safety and efficacy results

- Incidence of serious AEs was statistically significantly higher among subjects in the SMC group (22/1022 [2.2%]) than among those in the FCM group (6/996 [0.6%]) (p = 0.004)
- Occurrence of treatment-emergent AEs see Table 1
- Mean hemoglobin increases were greater in the FCM group than the SMC group, see Table 2
- No serious AEs were considered treatment-related

Table 1: Treatment-emergent AEs occurring in ≥ 2% of subjects in either treatment group or with a statistically significant difference[a] between the FCM or SMC treatment groups by anemia etiology (safety population).

	FCM		SMC	
System organ class[b]	**Postpartum (n = 606)**	**HMB (n = 390)**	**Postpartum (n = 623)**	**HMB (n = 399)**
Preferred term	n (%)	n (%)	n (%)	n (%)
≥1 treatment-emergent AE	143 (23.6)	129 (33.1)	150 (24.1)[c]	125 (31.3)[c]
Gastrointestinal disorders	13 (2.1)	21 (5.4)	66 (10.6)	71 (17.8)
General disorders and administration site conditions	43 (7.1)	44 (11.3)	1 (0.2)	11 (2.8)
Immune system disorders	3 (0.5)	2 (0.5)	0	0
Investigations	20 (3.3)	5 (1.3)	10 (1.6)[c]	1 (0.3)
Metabolism and nutrition disorders	1 (0.2)	7 (1.8)	1 (0.2)	0
Nervous system disorders	21 (3.5)	28 (7.2)	12 (1.9)[c]	9 (2.3)

[a] All comparisons between the FCM and SMC groups are statistically significant ($p \leq 0.05$) unless otherwise noted.
[b] Each subject is counted only once per system organ class.
[c] Not statistically significant from the FCM group.

Table 2: Mean hemoglobin and ferritin levels at baseline and at the highest level after randomization (safety population).

	FCM		SMC	
System organ class[b]	**Postpartum (n = 606)**	**HMB (n = 390)**	**Postpartum (n = 623)**	**HMB (n = 399)**
Hemoglobin, mean (SD), g/dL				
Baseline	10.20 (1.161)	9.34 (1.387)	10.11 (1.191)	9.40 (1.310)
Highest postrandomization result	12.53 (0.899)	11.68 (1.090)	11.97 (1.153)[a]	10.89 (1.246)[a]
Mean ferritin (SD), ng/mL				
Baseline	25.99 (22.730)	8.89 (15.529)	26.55 (24.973)	7.95 (15.072)
Highest postrandomization result	180.97 (96.798)	101.62 (89.312)	24.23 (16.743)[a]	20.94 (53.122)[a]

SD = standard deviation
[a] $p < 0.001$ for between-group comparison.

CONCLUSION

FCM was well tolerated and effectively increased mean hemoglobin levels in postpartum women or women with heavy menstrual bleeding and IDA.

Randomised trial comparing ferric carboxymaltose vs. oral ferrous glycine sulphate for postoperative anemia after total knee arthroplasty

E Bisbe, L Molto, R Arroyo, JM Muniesa, M Tejero
Brit J Anaesth 2014; 113(3): 402–409. doi:10.1093/bja/aeu092.
ClinicalTrials.gov number: NCT01913808

DESIGN

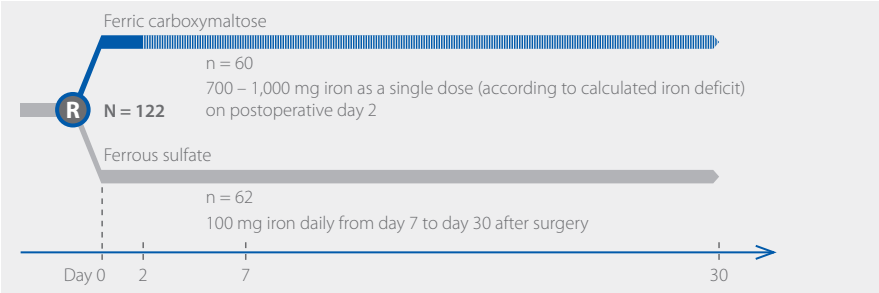
Prospective, randomised, single-blinded, controlled, phase IV trial (Sponsor: Vifor Pharma)

Patients (N = 122 randomised)

with postoperative anemia (without prior transfusions) after total knee arthroplasty (TKA)

Primary efficacy endpoints

Change in Hb level from postoperative day 4 to day 30 and percentage of patients without anemia (Hb > 12 g/dL)



RESULTS

Number of patients (ITT population)

- FCM: n = 59
- FS: n = 62

Main efficacy results

- Hb substantially decreased until day 4 in both groups, and partly recovered by day 30
- FCM-treated patients achieved Hb ≥ 12.0 g/dL more frequently (42.3% vs. 23.5%; p = 0.04) and showed a trend towards higher Hb increase from day 4 to day 30 (+1.7 [1.2] vs. +1.3 [1.0]; p = 0.075) compared with FS-treated patients
- Patients with postoperative Hb < 10 g/dL experienced better Hb increase with FCM (+2.4 [0.3] g/dL) than FS (+1.1 [0.4] g/dL; p = 0.018)
- Patients being iron-deficient at enrolment (56.7%) had a higher Hb increase with FCM (+1.9 [0.3] g/dL) than FS (+1.2 [0.2] g/dL; p = 0.03)
- Total EQ-5D and performance outcomes were comparable between the groups, but FCM was associated with better scores for 'usual activities'

CONCLUSION

In preoperatively non-anaemic TKA patients postoperative IV FCM provided significant benefit over oral FS, particularly in patients with preoperative iron deficiency, severe postoperative anemia, or both.

Clinical efficacy and safety of IV ferric carboxymaltose (FCM) treatment of RLS: A multi-centred, placebo-controlled preliminary clinical trial

RP Allen, CH Adler, W Du, A Butcher, DB Bregman, CJ Earley
Sleep Med 2011; 12: 906–913. doi:10.1016/j.sleep.2011.06.009
ClinicalTrials.gov number: NCT01382901

DESIGN

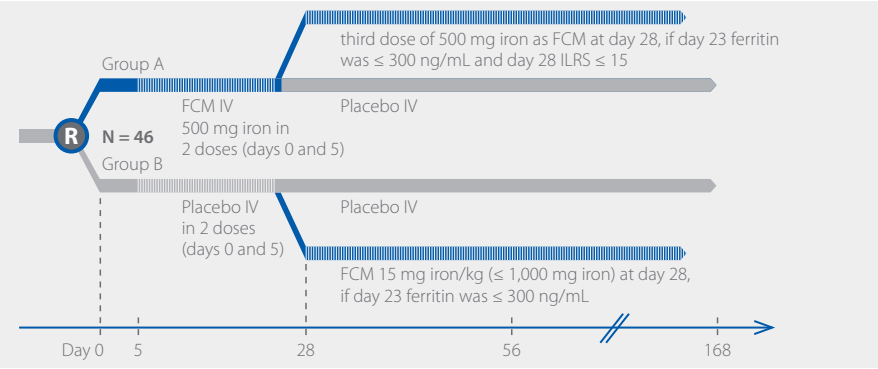
Randomised, double-blinded, placebo-controlled, parallel-group, phase II, multicentre study (Sponsor: Luitpold Pharmaceuticals)

Patients (N = 46 randomised)

with Restless Legs Syndrome (IRLS baseline score ≥ 15, RLS symptoms occurring ≥ 5 nights per week, actigraph measured PLMS average for 3 – 5 nights ≥ 15 h^{-1})

Primary outcome evaluation

Change of International Restless Legs Syndrome study group severity scale (IRLS)



RESULTS

Number of patients included in the treatment evaluation

- FCM: n = 24
- Placebo: n = 19

Main results

- FCM significantly improved primary and secondary outcomes compared to placebo:
  - International Restless Legs Syndrome study group severity scale (IRLS) average (SD) decrease of 8.9 (8.52) vs. 4.0 (6.11), $p = 0.040$
  - Clinical Global Inventory of Change (CGI-1) very much or much improved 48.3% vs. 14.3%, $p = 0.004$
  - QoL was also significantly improved
- Of the 24 with initial iron treatment 45% responded and 29% remitted (IRLS ≤ 10) at day 28, and 25% continued free of other RLS medications at 24 weeks after treatment
- The single 1,000 mg dose on day 28 produced the same degree of treatment response as the divided dose, but the added 500 mg dose for those not responding to the initial treatment showed little benefit
- There were no significant adverse events

CONCLUSION

IV FCM provided a well tolerated and effective treatment for RLS that lasted for at least 24 weeks for some patients.

Ferric carboxymaltose in patients with restless legs syndrome and nonanemic iron deficiency: a randomized trial

C Trenkwalder, J Winkelmann, W Oertel, G Virgin, B Roubert, A Mezzacasa, on behalf of the FCM-RLS Study Investigators
Mov Disord 2017; 32(10): 1478-1482. doi:10.1002/mds.27040
EudraCT number: 2013-000574-30

DESIGN

Randomised, patient- and assessor-blind, placebo-controlled, 12-week, Phase IV, multicentre study (Sponsor: Vifor Pharma)

Patients (N = 110 randomised) with

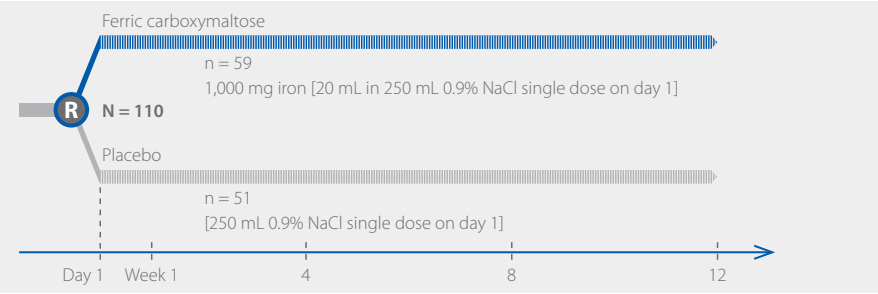
- moderate to severe RLS (IRLS total score ≥ 15)
- serum ferritin < 75 ng/mL (if serum ferritin ≥ 75 and < 300 ng/mL, patients with TSAT < 20% could be included)

Efficacy Endpoints

- Mean change in RLS symptom severity score from baseline to week 4, measured by IRLS, was the primary endpoint
- Mean changes from baseline to week 12 were defined as secondary endpoints, as measured by IRLS, CGI scale items-1 and -2, the Patient Global Impression of Improvement Index, RLS-6 scale, and QoL questionnaire

Safety

AEs were monitored throughout the study and up to 30 days after administration of treatment or study visit.



RESULTS

Number of patients (full analysis set):

- FCM: n = 59
- Placebo: n = 51

Main efficacy results

- **Primary endpoint:** Change in IRLS (LS mean) after 4 weeks: –7.7 (SE 1.1) for FCM vs –5.2 (SE 1.2) for placebo; non-significant treatment difference of –2.9 (95% confidence interval [CI] –5.93, 1.02; p = 0.163)
- **Secondary endpoints:** Significant improvements among patients treated with FCM compared to placebo:
  - in IRLS sum score (treatment difference –4.66 [95% CI –8.59, –0.73]; p = 0.021) at week 12
  - in RLS symptom severity (CGI scale item-1) from week 8 (treatment difference at week 8: –0.62 [95% CI –1.14, –0.09]; p = 0.023; at week 12: –0.70 [95% CI –1.25, –0.15]; p = 0.013)
  - in sleep satisfaction and daytime tiredness
- At week 12, there were significantly more responders among patients treated with FCM (37.3% vs 19.6% for placebo; p = 0.042), particularly for the proportion of patients achieving an IRLS score improvement of ≥ 6 points at any time during treatment (72.9% vs 47.1%; p = 0.006)

Main safety results

- 33 TEAEs were reported in 23 patients (FCM, 16 patients; placebo, 7 patients), the majority of which were mild or moderate in severity
- Severe TEAEs were reported in 4 patients in the FCM group and 2 with placebo
- Serious AEs were reported in 2 patients, 1 from each treatment group

CONCLUSION

Although the primary efficacy endpoint at week 4 was not met, a single 1,000 mg dose of FCM can provide significant improvements in RLS symptoms after 12 weeks in iron-deficient non-anaemic patients. FCM was well tolerated and no serious, treatment-related adverse events were reported.

Intravenous iron alone resolves anemia in patients with functional iron deficiency and lymphoid malignancies undergoing chemotherapy (FER-FID-CHEMO)

M Hedenus, T Karlsson, H Ludwig, B Rzychon, M Felder, B Roubert, G Birgegård
Med Oncol 2014; 31: 302. doi 10.1007/s12032-014-0302-3.
ClinicalTrials.gov number: NCT01101399

DESIGN

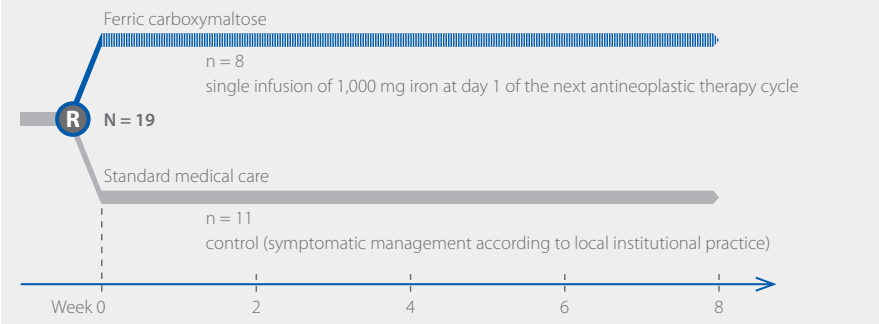
Prospective, randomised, open-label, controlled, phase III, multicentre study
(Sponsor: Vifor Pharma)

Patients (N = 19 randomised)

on treatment for indolent lymphoid malignancies, who had anemia and functional ID

Primary endpoint

Mean change in Hb from baseline to weeks 4, 6 and 8 without transfusions or ESA



RESULTS

- Difficulties with patient recruitment led to premature termination of the study
- 17 patients (8 FCM and 9 control) were included in the analysis
- In the FCM arm, mean Hb increase was significantly higher vs. control at week 8 ($p = 0.021$)
- All FCM-treated patients achieved an Hb increase > 1 g/dL (control 6/9; $p = 0.087$)
- TSAT was > 20% from week 2 onwards

CONCLUSION

FCM without ESA effectively increased Hb and iron status in patients with functional ID and lymphoid malignancies undergoing chemotherapy.

Pharmacokinetics and red cell utilisation of $^{52}Fe/^{59}Fe$-labelled iron polymaltose in anaemic patients using positron emission tomography

S Beshara, J Sörensen, M Lubberink, V Tolmachev, B Långström, G Antoni, BG Danielson, H Lundqvist
Br J Haematol 2003; 120: 853–859

DESIGN

Pharmacokinetic (PK) and pharmacodynamic (PD), phase I study (Sponsor: Vifor Pharma)

Patients (N = 6)

with ID, IDA, or renal anemia

Objective

To assess the pharmacokinetics and red cell utilization of iron polymaltose

A single IV injection of 100 mg iron as iron(III)-hydroxide-polymaltose complex*, labelled with a tracer in the form of $^{52}Fe/^{59}Fe$, was assessed using positron emission tomography (PET) for about 8 h. Red cell utilisation was followed for 4 weeks.

RESULTS

- Iron was similarly distributed to the liver, spleen and bone marrow. However, a larger proportion of this complex was rapidly distributed to the bone marrow
- The shorter equilibration phase for the liver (about 25 min), indicates the minimal role of the liver for direct distribution
- Splenic uptake reflected the reticuloendothelial handling of this complex
- Red cell utilisation ranged from 61% to 99% and was reached after 16–24 days. The high red cell utilization indicated the efficacy of this iron complex. Red cell utilisation was calculated as follows: Red cell utilization [%] on day n = WBA/ml on day n/injected 59Fe radioactivity x total blood volume [ml] x 100
- Red cell utilisation ranged from 61% to 99%
- Despite the relatively high uptake by the bone marrow, there was no saturation of marrow transport systems at this dose level

CONCLUSION

High red cell utilisation of iron polymaltose occurred in anaemic patients. Iron distributed to liver, spleen and bone marrow.

* iron(III)-hydroxide-polymaltose complex = ferric carboxymaltose = FCM

Safety and tolerability of intravenous ferric carboxymaltose in patients with iron deficiency anemia

G R Bailie, NA Mason, TG Valaoras
Hemodial Int 2010; 14: 47–54. doi: 10.1111/j.1542-4758.2009.00409.x

DESIGN

Randomised, double-blinded, placebo-controlled, multicentre, non-inferiority crossover, phase III study (Sponsor: Luitpold Pharmaceuticals)

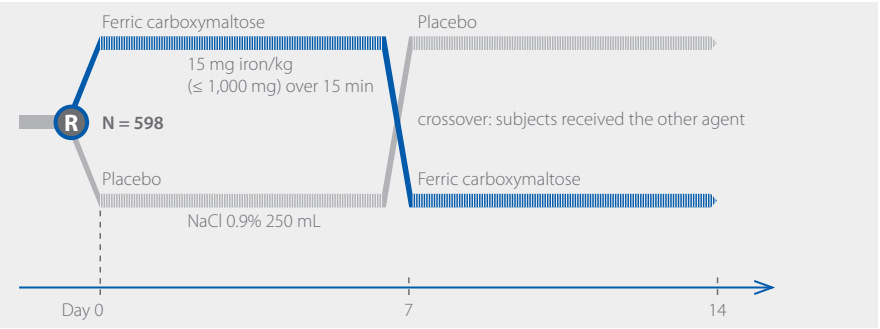
Patients (N = 598 randomised)

with IDA, assigned to 3 cohorts:

- Cohort I: IDA (TSAT ≤ 25% and serum ferritin < 300 ng/mL) secondary to anemia of CKD (including NDD-CKD, HD-dependent CKD, or peritoneal dialysis-dependent [PDD-CKD])
- Cohort II: IDA (TSAT ≤ 25% and serum ferritin < 300 ng/mL) secondary to IBD
- Cohort III: IDA (TSAT ≤ 25% and serum ferritin ≤ 100 ng/mL) secondary to other conditions

Primary endpoint

Incidence of TEAEs during each 7-day study period



RESULTS

Number of patients

- Safety population (patients who received at least 1 dose of iron or placebo): n = 582
- Completer population (patients who had both doses attempted): n = 559

TEAEs

≥ 1 TEAE during the First 24 hours		≥ 1 TEAE during 7-day treatment period	
FCM	Placebo	FCM	Placebo
15.0%	11.4%	29.3%	19.7%

- Most TEAEs were classified as Grade 1 or 2
- Six subjects had Grade 3 treatment-emergent adverse events after FCM and 9 subjects after placebo
- One subject had a Grade 4, and 1 subject had a Grade 5 treatment-emergent adverse event, but neither was considered study drug-related

CONCLUSION

Administration of FCM (15 mg/kg, ≤ 1,000 mg) over 15 minutes was well tolerated and associated with minimal risk of adverse reactions in patients with iron deficiency anemia.

Pharmacokinetics, safety and tolerability of intravenous ferric carboxymaltose: a dose-escalation study in volunteers with mild iron-deficiency anemia

P Geisser, J Banké-Bochita
Arzneimittelforschung 2010; 60(6a): 362–372

DESIGN

Randomised, double-blind, placebo-controlled, single-dose, dose-escalating, phase I, single-centre study (Sponsor: Vifor Pharma)

Patients (N = 32 randomised)

with mild IDA (Hb 9.0 – 12.0 g/dL in women, or 9.0 – 13.0 g/dL in men serum ferritin < 20 ng/mL, TSAT < 16%)

Objective

Investigation of PK, PD, safety and tolerability of single, escalating doses of FCM

N = 32

- 100 mg iron given as an IV bolus injection (n = 8)
- 500 mg iron given as IV infusion over 15 min (n = 8)
- 800 mg iron given as IV infusion over 15 min (n = 8)
- 1,000 mg iron given as IV infusion over 15 min (n = 8)

} At each dose level 6 patients received FCM and 2 received placebo

RESULTS

Number of patients (safety and PK/PD population: N = 32)

Main results

- Compared with placebo, a rapid, dose-dependent increase in total serum iron was observed across all dose groups. Mean (standard deviation) maximum total serum iron levels ranged between 36.9 (4.4) and 317.9 (42.3) ng/mL in the 100 and 1,000 mg groups
- Concentration-time curves of total serum iron continuously declined for up to 24 and 72 h post-dose in the 100 and 500 – 1,000 mg groups, respectively
- FCM was cleared from the serum with a terminal elimination half-life between 7,4 and 12,1 hours
- A dose-dependent, but not dose-linear, increase in serum ferritin was seen in all treatment groups compared with placebo, with peak levels of a 23 – 210-fold increase above baseline occurring 48 – 120 h post dose
- Iron-binding capacity was transiently almost fully utilised after doses of 500, 800 and 1,000 mg (TSAT > 95%)
- No meaningful changes in serum transferrin or serum transferrin receptor concentrations were observed during this study

CONCLUSION

The majority of FCM was or eliminated from blood within 24 h of administration of a 100 mg dose and within 72 h of a 500 – 1,000 mg dose. FCM was generally well tolerated across all doses in patients with mild IDA. This study demonstrates that the good safety and PK profile of FCM provides patients with the full therapeutic benefit of a parenteral iron replacement treatment.

Direct comparison of the safety and efficacy of ferric carboxymaltose versus iron dextran in patients with iron deficiency anemia

I Hussain, J Bhoyroo, A Butcher, TA Koch, A He, DB Bregman
Anemia 2013; 2013: 169107. doi: 10.1155/2013/169107.
ClinicalTrials.gov number: NCT00704028

DESIGN

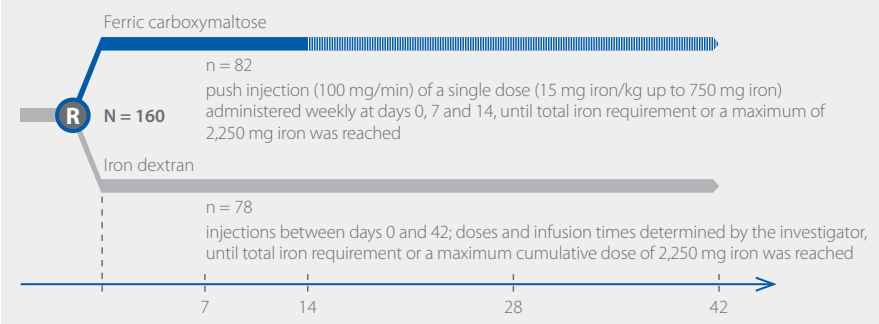
Randomised, open label, phase IIIb, multicentre study over 7 weeks
(Sponsor: Luitpold Pharmaceuticals)

Patients (N = 161 randomised)

with IDA and baseline Hb of ≤ 11 g/dL

Primary endpoint

Incidence of TEAEs from day 0 to day 42, or 28 days after the last dose of study drug



RESULTS

Number of patients (modified ITT population)

- FCM: n = 77
- DEX: n = 69

Main results

- In the FCM arm, the change in Hb from baseline to the highest observed level was 2.8 g/dL, whereas the DEX arm displayed a change of 2.4 g/dL (p = 0.20)
- Adverse events, including immune system disorders (0% in FCM versus 10.3% in DEX, p = 0.003) and skin disorders (7.3% in FCM versus 24.4% in DEX, p = 0.004), were less frequently observed in the FCM group

CONCLUSION

Treatment of IDA with FCM resulted in fewer hypersensitivity-related reactions than DEX.

FCM is a well tolerated, effective and convenient option for the treatment of IDA of any aetiology.

Safety and efficacy of intravenous ferric carboxymaltose (750 mg) in the treatment of iron deficiency anemia: Two randomised, controlled trials

CF Barish, T Koch, A Butcher, D Morris, DB Bregman
Anemia 2012; 2012: 172104. doi: 10.1155/2012/172104.
ClinicalTrials.gov number: NCT00703937 and NCT00704353

DESIGN

Two randomised, open-label, placebo-controlled, phase III trials
(Sponsor: Luitpold Pharmaceuticals)

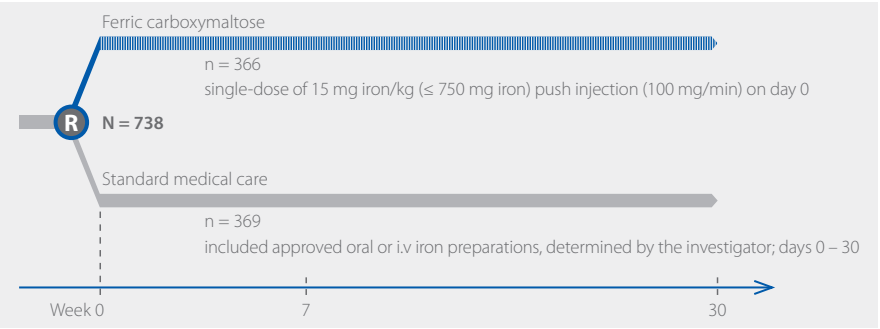
Patients (N = 738 [Single-dose]/708 [Multidose] randomised)

with IDA (Hb ≤ 12 g/dL, ferritin ≤ 100 or ≤ 300 ng/mL with TSAT ≤ 30%)

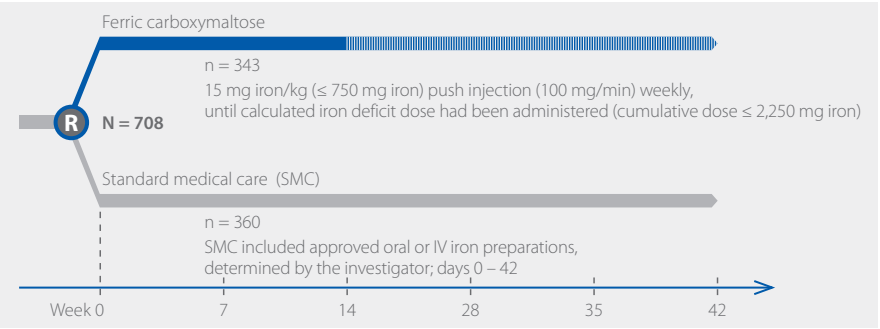
Objective

- Primary objective: to evaluate the safety of a maximum administered dose of 750 mg of FCM compared to SMC in the treatment of IDA
- Secondary objectives: improvements in hemoglobin and iron indices

Single-dose study



Multidose study



RESULTS

Number of patients

- Safety population

	FCM	SMC
Single-dose study	366	369
Multidose study	343	360

- Modified ITT population (efficacy analyses summarised for the following treatment groups):
  - FCM: n = 293
  - IS and sodium ferric gluconate: n = 103
  - Oral iron: n = 152
  - Other treatment: n = 42

Main results

- Significantly greater ($p \leq 0.001$) increases in Hb and iron indices occurred in FCM groups versus SMC
- In the multidose study, up to two infusions of FCM were needed to reach target iron levels versus 3 – 5 of IV iron comparators
- FCM and SMC groups had similar incidences and types of adverse events and serious adverse events

CONCLUSION

IV FCM is well tolerated and associated with improvements in Hb and iron indices comparable to SMC when administered in single doses of up to 750 mg at a rate of 100 mg/min. Fewer FCM infusions were required to reach target iron levels compared to other IV iron preparations.

A multicentre, randomised, active-controlled study to investigate the efficacy and safety of intravenous ferric carboxymaltose in patients with iron deficiency anemia

JE Onken, DB Bregman, RA Harrington, D Morris, P Acs, B Akright, C Barish, BS Bhaskar, GN Smith-Nguyen, A Butcher, TA Koch, LT Goodnough
Transfusion 2014; 54: 306–315. doi: 10.1111/trf.12289.
ClinicalTrials.gov number: NCT00982007

DESIGN

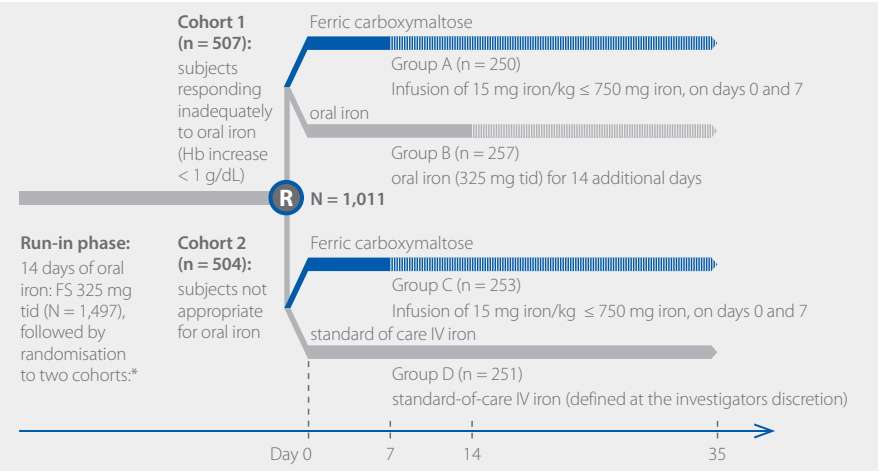
Randomised, open-label, active-controlled, phase III, multicentre trial
(Sponsor: Luitpold Pharmaceuticals)

Patients (N = 1,497 enrolled)

with IDA

Primary efficacy endpoint

Change to highest observed Hb from baseline to day 35



* Study participants who responded adequately to oral iron during run-in (Hb increase ≥ 1 g/dL) were not randomised

RESULTS

Number of patients (modified ITT population)

- Group A: n = 244
- Group B: n = 251
- Group C: n = 245
- Group D: n = 237

Main efficacy results

- Mean (± SD) Hb increase (primary endpoint) was significantly greater in Group A-FCM than Group B-oral iron: 1.57 (± 1.19) g/dL vs. 0.80 (± 0.80) g/dL (p = 0.001)
- Post hoc comparison of Group C-FCM and Group D-IV standard of care also demonstrated significant mean (± SD) increase in Hb from baseline to highest value by day 35 in Group C vs. Group D: 2.90 (± 1.64) g/dL vs. 2.16 (± 1.25) g/dL (p = 0.001)

CONCLUSION

Two 750 mg FCM infusions are well tolerated and superior to oral iron in increasing Hb levels in IDA patients with inadequate oral iron response.

Ferinject® ▼ (ferric carboxymaltose)
Prescribing Information – UK
For full prescribing information refer to the Summary of Product Characteristics (SmPC)
Active ingredient: Ferric carboxymaltose (50 mg/mL) **Presentation:** Solution for injection/infusion. Available as a 2mL vial (as 100 mg of iron), 10 mL vial (as 500 mg of iron) and 20 mL vial (as 1,000 mg of iron). **Indication:** Treatment of iron deficiency when oral iron preparations are ineffective or cannot be used. The diagnosis must be based on laboratory tests. **Dosage and Administration:** The posology of Ferinject follows a stepwise approach: Step 1: Determination of the iron need; The individual iron need for repletion using Ferinject is determined based on the patient's body weight and haemoglobin (Hb) level. The table in the SmPC should be used to determine the iron need. Step 2: Calculation and administration of the maximum individual iron dose(s); Based on the iron need determined, the appropriate dose(s) of Ferinject should be administered: A single Ferinject administration should not exceed: • 15 mg iron/kg body weight (for administration by intravenous injection) or 20 mg iron/kg body weight (for administration by intravenous infusion). The maximum recommended cumulative dose of Ferinject is 1,000 mg of iron (20 mL Ferinject) per week. Administration rates for intravenous injection: For iron doses of 100 mg to 200 mg, there is no prescribed administration time. For doses >200 mg to 500 mg, Ferinject should be administered at a rate of 100 mg iron/min. For doses >500 mg to 1,000 mg, the minimum administration time is 15 min. Administration of intravenous drip infusion: For iron doses of 100 mg to 200 mg, there is no prescribed administration time. For doses >200 mg to 500 mg, Ferinject should be administered in a minimum of 6 mins. For doses >500 mg to 1,000 mg, the minimum administration time is 15 mins. Ferinject must be diluted in 0.9% m/V NaCl but not diluted to concentrations less than 2 mg iron/mL. Step 3: Post-iron repletion assessments **Contraindications:** Hypersensitivity to Ferinject or any of its excipients. Known serious hypersensitivity to other parenteral iron products. Anaemia not attributed to iron deficiency. Iron overload or disturbances in utilisation of iron. **Special warnings and precautions:** Parenterally administered iron preparations can cause potentially fatal anaphylactic/anaphylactoid reactions. The risk is enhanced for patients with known allergies, a history of severe asthma, eczema or other atopic allergy, and in patients with immune or inflammatory conditions. Ferinject should only be administered in the presence of staff trained to manage anaphylactic reactions where full resuscitation facilities are available (including 1:1000 adrenaline solution). Each patient should be observed for 30 minutes following administration. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Parenterally administered iron preparations can cause hypophosphataemia which in most cases is transient and without clinical symptoms. Cases of hypophosphataemia requiring medical attention were reported, mainly in patients with existing risk factors and after prolonged exposure to high-dose intravenous iron. In patients with liver dysfunction, parenteral iron should only be administered after careful risk/benefit assessment. Careful monitoring of iron status is recommended to avoid iron overload. There is no safety data on the use of single doses of more than 200mg iron in haemodialysis-dependent chronic kidney disease patients. Parenteral iron must be used with caution in case of acute or chronic infection, asthma, eczema or atopic allergies. It is recommended that treatment with Ferinject is stopped in patients with ongoing bacteraemia. In patients with chronic infection a benefit/risk evaluation has to be performed. Caution should be exercised to avoid paravenous leakage when administering Ferinject. **Special populations:** The use of Ferinject has not been studied in children. A careful risk/benefit evaluation is required before use during pregnancy. Ferinject should not be used during pregnancy unless clearly necessary and should be confined to the second and third trimester. **Undesirable effects:** Common (≥1/100 to <1/10): Hypophosphataemia, headache, dizziness, flushing, hypertension, nausea, injection/infusion site reactions. Please consult the SmPC in relation to other undesirable effects. **Legal category:** POM. **Price:** pack of 5 x 2 ml = £81.18; pack of 5 x 10 ml = £405.88 pack of 1 x 20 ml = £154.23. **MA Number:** 15240/0002. **Date of Authorisation:** 19.07.2007. **MA Holder:** Vifor France, 100-101 Terrasse Boieldieu, Tour Franklin La Défense 8, 92042 Paris La Défense Cedex, France. **Further details available from:** Vifor Pharma UK Limited, The Old Stables, Bagshot Park, Bagshot, Surrey GU19 5PJ T: +44 1276 853 600 F: +44 1276 452 341 medicalInfo_UK@viforpharma.com
Ferinject® is a registered trademark. Date of revision: 12/2018.

Adverse events should be reported.
Reporting forms and information can be found at www.mhra.gov.uk/yellowcard
Adverse events should also be reported to Vifor Pharma UK Ltd. Tel: +44 1276 853633

HQ-FCM-1900069

NOTIZEN