Efficacy and safety of ferric carboxymaltose in correcting iron-deficiency anemia: a review of randomized controlled trials across different indications

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Abstract

Ferric carboxymaltose (FCM, Ferinject®) was effective and well tolerated in the treatment of iron-deficiency anemia (IDA) in nine, Phase III, randomized, controlled, multicenter trials in a diverse range of indications, including patients with inflammatory bowel disease (IBD), post-partum anemia (PPA) or abnormal uterine bleeding (AUB), chronic heart failure (CHF), non-dialysis-dependent chronic kidney disease (CKD) and those undergoing hemodialysis (HD).

In most trials, patients received either FCM doses of ≤1000 mg, administered intravenously (i.v.) over ≤15 min., or oral ferrous sulfate (FeSulf) 325 mg (65 mg iron), three times daily (t.i.d.), or 304 mg (100 mg iron), twice daily (b.i.d.). In one trial, patients on HD received 200 mg i.v. of either FCM or iron sucrose (ISC), two to three times weekly. In a pilot study in patients with CHF and CKD, patients received 200 mg of FCM by push injection compared with 200 mg of ISC slow injection. FCM was usually administered until the patient's calculated total iron replacement dose was achieved.

Treatment with FCM improved indices of anemia (hemoglobin [Hb], ferritin and transferrin saturation [TSAT] values). In patients on HD with IDA secondary to CKD, FCM demonstrated comparable efficacy to ISC in achieving an increase in Hb. In patients with IBD or PPA, improvements in Hb levels were more rapid with FCM than with FeSulf. Patients with PPA receiving FCM compared with those receiving oral iron achieved an Hb rise ≥2.0 g/dl earlier (7 days compared with 14 days; p < 0.001), were more likely to achieve an Hb rise ≥3.0 g/dl at any time beginning at day 14 (86.3% compared with 60.4%; p < 0.001), and achieve an Hb >12.0 g/dl at the end of the study (Day 42; 90.5% compared with 68.6%, p < 0.01). Serum ferritin increased in the i.v. FCM treatment group, but not in the oral iron group. Differences between groups were significant at each study interval. TSAT increased significantly at every interval in both groups; however, FCM-treated patients showed higher TSAT at each interval after the first week. FCM improved patient quality of life to an equivalent extent to oral FeSulf in patients with IBD or PPA, and to a greater extent than oral FeSulf in women with AUB. FCM also improved quality of life as well as functional symptoms and exercise capacity in patients with CHF. Safety data from more than 3000 patients showed that FCM was well tolerated. No safety concerns have been identified in breastfed infants of mothers receiving FCM. FCM is, therefore, an effective and well-tolerated option in the treatment of IDA.

Key words

- Anemia
- Ferinject®
- Ferric carboxymaltose, efficacy, safety
- Intravenous iron
- Iron deficiency

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1. Introduction

Iron(III)-hydroxide polymaltose complex (ferric carboxymaltose, FCM; Ferinject®, Vifor (International) Inc., St. Gallen, Switzerland) is a novel, next-generation complex for intravenous (i.v.) iron treatment, developed to reduce the limitations of previous i.v. iron preparations such as high pH, high osmolarity, long administration time, or dosage limitations [1]. FCM does not react with dextran antibodies, has a pH between 5.0 and 7.0, and up to 1000 mg iron (as FCM) can be infused within 15 min [1]. FCM has a unique carboxymaltose shell, which leads to a highly stable, type I polynuclear iron (III)-hydroxide carbohydrate complex [1], with a molecular mass of approximately 150,000 Daltons. FCM releases minimal amounts of iron into the circulation. The iron is taken up in a controlled way by the macrophages, and delivered to transferrin and ferritin via the physiological iron metabolism pathways.

To date, the safety and efficacy of FCM in correcting iron deficiency have been investigated in a diverse range of indications in ten completed Phase I—III studies. The key findings of the following nine published Phase III studies will be discussed in this review:

- iron-deficiency anemia (IDA) secondary to inflammatory bowel disease (IBD) [2]
- post-partum IDA [3—5]
- IDA from abnormal uterine bleeding (AUB) [6]
- IDA in patients with non-dialysis-dependent chronic kidney disease (NDD-CKD) [7]
- IDA associated with maintenance hemodialysis (HD) [8]
- IDA in patients with chronic heart failure (CHF) [9]
- IDA in patients with a variety of chronic conditions including NDD-CKD, HD-dependent CKD, peritoneal dialysis-dependent CKD and IBD [10].

2. FCM in the management of IDA secondary to IBD [2]

Anemia is a frequent complication of IBD (Crohn's disease [CD] and ulcerative colitis [UC]) [2, 11]. The cause of iron deficiency has been attributed to chronic blood loss from the ulcerated intestinal mucosa, and to impairment of iron intake and uptake, resulting in a negative iron balance [2, 12]. In active disease, inflammatory mediators may alter iron metabolism (by retaining iron in the reticular-endothelial system), erythropoiesis, and erythrocyte survival. This condition is termed anemia of chronic disease. Iron supplementation should be initiated when IDA is present [13].

In recent years, the use of oral iron replacement therapy for IBD has been questioned. Iron absorption may be compromised in patients with IBD, making oral iron therapy ineffective in patients with ongoing iron loss [2]. Intolerance and discontinuation due to adverse events (AEs) with oral iron are frequent [11]. In contrast, i.v. iron replacement, particularly with iron sucrose (ISC; Venofer®, Vifor (International) Inc.) has been found to be effective and well tolerated [14], although a potential disadvantage is the need for repeated infusions and long infusion times; single doses should not exceed 500 mg iron per infusion per week, infused over at least 3.5 h. This requires repeated hospital visits by the patient, therefore consuming both time and resources.

Consequently, a multicenter, open-label, randomized, controlled study was conducted by Kulnigg et al. [2] to establish the non-inferiority and safety of FCM in comparison with oral ferrous sulfate (FeSulf) in reducing IDA (defined by hemoglobin [Hb] ≤ 10.0 g/dl and transferrin saturation [TSAT] < 20% or serum ferritin < 100 μg/l) secondary to chronic IBD (CD or UC).

Two hundred adult patients (aged 18—80 years) were randomized in a 2:1 ratio (FCM, n = 137; FeSulf, n = 63) to receive FCM (maximum 1000 mg iron per infusion and no more than three infusions permitted per treatment cycle) at 1-week intervals until the patients’ calculated total iron deficit (Ganzoni equation) [15] was

Abbreviations

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<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>ADE</td>
<td>adverse drug event</td>
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<td>AE</td>
<td>adverse event</td>
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<td>AUB</td>
<td>abnormal uterine bleeding</td>
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<td>b.i.d.</td>
<td>twice daily</td>
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<td>CD</td>
<td>Crohn’s disease</td>
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<td>chronic heart failure</td>
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<td>CKD</td>
<td>chronic kidney disease</td>
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<td>ESA</td>
<td>erythropoiesis-stimulating agent</td>
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<tr>
<td>FAIR-HF</td>
<td>Ferinject® Assessment in patients with Iron deficiency and chronic Heart Failure</td>
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<td>FCM</td>
<td>ferric carboxymaltose</td>
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<td>FeSulf</td>
<td>ferrous sulphate</td>
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<td>GI</td>
<td>gastrointestinal</td>
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<td>Hb</td>
<td>hemoglobin</td>
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<td>HD</td>
<td>hemodialysis</td>
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<td>HD-CKD</td>
<td>hemodialysis-dependent chronic kidney disease</td>
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<td>i.v.</td>
<td>intravenous</td>
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<td>IBD</td>
<td>inflammatory bowel disease</td>
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<td>IDA</td>
<td>iron-deficiency anemia</td>
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<td>ISC</td>
<td>iron sucrose</td>
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<td>ITT</td>
<td>intention-to-treat</td>
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<td>NDD-CKD</td>
<td>non-dialysis-dependent chronic kidney disease</td>
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<td>NYHA</td>
<td>New York Heart Association</td>
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<td>per-protocol</td>
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<td>PPA</td>
<td>post-partum anemia</td>
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<td>QoL</td>
<td>quality of life</td>
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<td>SF-36</td>
<td>36-item short-form questionnaire</td>
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<td>t.i.d.</td>
<td>three times daily</td>
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<td>TEAE</td>
<td>treatment-emergent adverse event</td>
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<td>TIBC</td>
<td>total iron-binding capacity</td>
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<td>TSAT</td>
<td>transferrin saturation</td>
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<td>UC</td>
<td>ulcerative colitis</td>
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31 The single maximum dosage may vary from country to country; refer to local Summary of Product Characteristics for more prescribing information.
reached, or 304 mg FeSulf (100 mg iron) orally, twice daily (b.i.d.) for 12 weeks. The primary endpoint was change in Hb from baseline to week 12. Exclusion criteria were: untreated vitamin B₁₂ or folate deficiency, other types of anemia, erythropoietin treatment within 8 weeks prior to enrollment, and iron replacement therapy or blood transfusion within the previous 30 days. Concomitant medication use was recorded, but erythropoietin treatment was not permitted during the study.

Quality of life (QoL) (assessed using the 36-item short-form questionnaire [SF-36]) and disease activity were determined at baseline and every 4 weeks.

The median calculated iron deficit was 1405 mg (range 937–2102 mg) in the FCM group and 1392 mg (range 982–1927 mg) in the FeSulf group. The median Hb improved from 8.7 to 12.3 g/dl in the FCM group and from 9.1 to 12.1 g/dl in the FeSulf group; non-inferiority was demonstrated (intention-to-treat [ITT] analysis: p = 0.6967; per protocol [PP] analysis: p = 0.8016).

Secondary efficacy endpoints included: change in Hb, serum ferritin and TSAT from baseline to weeks 2, 4, 8, and 12; number and proportion of patients who achieved target levels of Hb, ferritin, and TSAT at weeks 2, 4, 8, and 12; proportion of patients discontinuing due to lack of response, QoL, and disease activity). AEs and concomitant medications were recorded at each visit.

Response (defined as the proportion of patients with an Hb increase of >2.0 g/dl) was faster for patients in the FCM group than those in the FeSulf group at week 2 (p = 0.0051) and week 4 (p = 0.0346). The statistical analysis of the cumulative Hb responder rate over 12 weeks demonstrated a statistically significant difference between the treatment groups (log-rank test, p = 0.0009). Median ferritin increased from 5.0 to 323.5 µg/l at week 2, and decreased to 43.5 µg/l at week 12. In the FeSulf group, a moderate increase from 6.5 to 28.5 µg/l at week 12 was observed. The final percentage of responders (defined as the proportion of patients with serum ferritin within target levels of 100–800 µg/l) at week 12 was 26.5% in the FCM group versus 3.3% in the FeSulf group (Kaplan-Meier analysis: log-rank test, p < 0.001).

TSAT increased in both groups, from 4% to 23% in patients treated with FCM, and from 6% to 17% in patients treated with FeSulf. The percentage of responders (defined as the proportion of patients with 20–50% TSAT) was significantly higher in the FCM group at week 2 (p = 0.0006) and week 4 (p = 0.0130), but the point estimates at week 12 appeared similar. Analyses over the 12-week period, however, showed statistically significant differences between the two groups (log-rank test, p = 0.0086).

There was an improvement in QoL in both groups, with a slightly higher median change from baseline in the SF-36 total score in the FCM group than in the FeSulf group at all time points (+14 versus +8.6 at week 12) [2]. Both the Crohn’s Disease Activity Index and the Collitis Activity Index showed decreases in mean total scores during the study in both treatment groups, indicating that FCM may also improve QoL.

FCM was well tolerated, and the dosing schedule was not associated with any clinically relevant safety concerns. Treatment-related AEs were experienced by 28.5% and 22.2% of patients in the FCM and FeSulf groups, respectively. A higher proportion of patients in the FeSulf group discontinued study medication due to an AE (2 [1.5%] patients in the FCM group versus 5 [7.9%] patients in the FeSulf group, Fisher’s Exact test, p = 0.033). There were no cases of anaphylactic shock/reaction.

In summary, FCM was effective in the treatment of IBD-associated IDA, providing a fast increase in Hb levels and the refill of iron stores, and allowing convenient administration of up to 1000 mg iron within 15 min. FCM may also improve patient QoL.

This study had an open design, but the main outcome parameter for the trial was an objective measure (Hb increase) and is thus unlikely to be influenced by a non-blinded trial. However, subjective parameters, such as QoL or disease activity scores might have been influenced by patient perception and observer bias. The number of patients who discontinued treatment due to AEs was unexpectedly low, as intolerance of FeSulf is expected to occur in approximately 25% of patients with IBD [16]. As patients with a history of iron intolerance were excluded, selection bias for iron-tolerant patients may play a role in these findings.

FCM offers a convenient treatment option for IBD-associated anemia. To simplify the therapeutic scheme further, additional trials on the use of FCM for the simple and pragmatic correction of anemia in IBD are currently ongoing, and results are expected in 2010 (clinicaltrials.gov).

3, Post-partum IDA and FCM [3–5]

Post-partum anemia (PPA) arises frequently, imposes a substantial disease burden during critical periods of maternal–infant interaction and may give rise to lasting developmental deficits in infants of affected mothers [5, 17]. Iron deficiency is a common cause of anemia in the post-partum period [18]. Oral treatment with FeSulf has been considered the standard of care in PPA. However, parenteral iron treatment is expected to be advantageous in cases in which treatment with oral iron is not possible due to gastrointestinal (GI) AEs, in patients with poor compliance, or in patients with severe anemia [3].

Three randomized, open-label, controlled studies have been conducted to compare the efficacy of large-dose i.v. FCM (total iron dose was calculated using the Ganzoni formula, modified to include adjustment for baseline iron status) [15] versus oral FeSulf in women with IDA (defined as Hb ≤10.5 g/dl) within the 10-day post-partum period [3–5] (Table 1),...
In the first non-inferiority study undertaken by Van Wyck et al. [5], patients (aged 15–49 years) received either i.v. FCM (≤1000 mg iron over 15 min, repeated weekly to achieve a total calculated iron replacement dose) or FeSulf (325 mg [65 mg iron], orally, three times daily [t.i.d.] for 6 weeks) (Table 1). Patients with Hb ≤10.0 g/dl were enrolled; patients were excluded if they had demonstrated previous non-adherence to prescribed oral iron therapy, active severe infection, serum TSAT >50%, serum ferritin >500 μg/l, received erythropoiesis-stimulating agents (ESAs) within 3 months of screening, a history of myelosuppressive therapy, or an hematological disorder other than iron deficiency. Premature withdrawal was required if an alternative intervention for the management of anemia was given. Red blood cell transfusion, initiation of ESAs or iron administration were not included in the study protocol.

One-hundred and seventy-four patients received 350 doses of i.v. FCM (mean total dose 1403 mg) in three, two, or one injections (19 [10.9%], 138 [79.3%] or 17 [9.8%] of patients, respectively); 178 patients received FeSulf. To estimate sample size, 80% of patients in each treatment group were assumed to be compliant with dosing and achieve the primary endpoint. Based on this assumption, a sample size of 160 patients per treatment group provided 85% power to achieve a 97.5% two-tailed lower confidence bound >15% for the treatment difference (i.v. iron minus oral iron) in success rate. Health-related QOL was assessed using normalized data from the SF-36 questionnaire [19] and the Fatigue Linear Analogue Scale Assessment [20].

The primary efficacy endpoint was the proportion of patients with an Hb increase ≥2.0 g/dl post-treatment. There was no between-group difference in the proportion of patients who achieved a rise in Hb ≥2.0 g/dl at day 42 (96.4% versus 94.1%; p = 0.443). FCM was non-inferior to oral FeSulf (Fig. 1A). Adherence to prescribed therapy was greater among patients in the i.v. FCM group compared with those in the oral FeSulf group (mean adherence 98.0% versus 83.9%).

Secondary efficacy endpoints included the proportion of patients attaining an Hb increase ≥2.0 g/dl and an Hb level ≥12.0 g/dl (correction of anemia; normal value used to assess response), time to achieve primary outcome, peak Hb increase from baseline, time to peak Hb increase, maximal increase in serum ferritin, TSAT, reticulocyte count, number of patients requiring intervention, time to intervention, proportion of patients with an Hb increase ≥2.0 g/dl and serum ferritin ≥160 μg/l, and the proportion of patients with improved QOL. Patients receiving i.v. FCM were more likely to achieve an Hb rise ≥3.0 g/dl at any time from day 14 onwards during the study than those receiving FeSulf (p < 0.001; the proportion of responders at day 42 were 86.3% versus 60.4%) (Fig. 1B). Patients receiving i.v. FCM were more likely to achieve an Hb level ≥12.0 g/dl at the end of the study (day 42) than those receiving FeSulf (90.5% versus 68.6%, p < 0.01) (Fig. 1C). Patients assigned to i.v. FCM achieved an Hb rise ≥2.0 g/dl sooner than those assigned to oral FeSulf (median time to achieve primary endpoint: 7 days compared with 14 days, respectively, p < 0.001).

Among patients assigned to i.v. FCM, overall erythropoietic response (Hb, hematocrit, reticulocytes, mean corpuscular volume, mean corpuscular Hb and reticulocyte Hb content) was more robust at most treatment intervals than for patients treated with FeSulf.

Serum ferritin increased rapidly in the i.v. FCM treatment group, but did not increase in the oral FeSulf group (Fig. 1D). Importantly, the serum ferritin level was in the normal range at the end of the study in the FCM group. Differences between groups were significant at each study interval. TSAT increased significantly and at every interval in both groups, related to a rise in serum iron and a fall in total iron-binding capacity (TIBC). Patients treated with i.v. FCM showed higher
Fig. 1: Percentage of patients with post-partum anemia (PPA) achieving anemia endpoints according to treatment assignment (i.v. ferric carboxymaltose [FCM] ≤ 1000 mg over 15 min given on days 0, 7 and 14, or oral FeSulf [325 mg, equivalent to 65 mg iron] twice daily, on days 0–42). A) Primary study endpoint, Hb ≥ 2.0 g/dl; B) secondary endpoint, Hb increase ≥ 2.0 g/dl; C) secondary endpoint achieved, Hb ≥ 12.0 g/dl; D) Change in markers of iron status (serum ferritin) from baseline according to treatment assignment in patients with PPA [5].

Between-group comparisons. *p < 0.05; **p < 0.01; ***p < 0.001.

Solid line with circle, i.v. FCM; solid line with triangle, oral FeSulf.


TSAT than patients treated with FeSulf at each interval after the first week, associated with a more pronounced rise in serum iron and fall in TIBC. No patient in either treatment group received red blood cell transfusion. Patient QoL increased in both treatment groups; between-group differences were not significant. The within-group change from baseline to day 42 met or exceeded criteria for the minimum important difference for every health-related QoL scale except SF-36 Role-Emotional.

Information on the efficacy of oral FeSulf in PPA in the current trial was restricted to 42 days of administration. Longer trials will be needed to confirm whether the higher iron stores achieved in patients treated with i.v. iron signify a persistent treatment benefit in women with ongoing menses or subsequent pregnancy.

In the second non-inferiority study, conducted by Breymann et al. [3], patients (aged 18–44 years) with PPA (Hb ≤ 10.5 g/dl) were randomized (2:1 ratio) to receive i.v. FCM over 2 weeks (up to three weekly doses of 1000 mg iron, maximum, per dose, given in 15 min; maximum of three infusions; n = 227) or 304 mg FeSulf (100 mg of iron), orally, b.i.d., for 12 weeks (n = 117). Changes in Hb and iron stores up to week 12 were analyzed (Table 1). Patients with anemia other than that caused by blood loss secondary to delivery and iron deficiency were excluded from the study. The planned sample size of 348 patients was based on a 90% power
to detect non-inferiority using a margin of 5.0 g/l and alpha of 0.025 (one-sided) and expected standard deviation of 12.0 g/l, with a 20% drop-out rate. The mean calculated iron deficit was 1365 mg (range 720—2024) and 1393 mg (range 829—1918) in the FCM and oral FeSulf groups, respectively (PP population).

Primary efficacy endpoint was the change from baseline to week 12 in Hb levels. Intravenous FCM was as effective as FeSulf in increasing Hb, despite the much shorter treatment period. Mean Hb changes from baseline to week 12 were 33.7 g/l and 32.9 g/l in the FCM and FeSulf treatment groups, respectively (Fig. 2).

Secondary efficacy endpoints included change from baseline in ferritin and TSAT; response rate of patients achieving Hb levels of 12.0—16.0 g/dl, ferritin levels of 50—800 µg/l, TSAT levels of 20—50%; and the number and proportion of patients who needed transfusions. Ferritin levels were significantly higher in patients treated with i.v. FCM than in patients treated with oral FeSulf (p < 0.0001). Mean ferritin levels increased from 39.9 µg/l at baseline to 568.2 µg/l at week 1 for patients in the FCM group. A decrease was seen in following weeks, but ferritin levels remained above baseline at all visits (mean: 161.2 µg/l at week 12). Patients in the FeSulf group showed only a marginal ferritin increase from 32.4 µg/l at baseline to 43.3 µg/l at visit 2 (p < 0.0001). Changes from baseline in mean TSAT values were significantly higher in the FCM group compared with the FeSulf group at all visits (p ≤ 0.0004). Response rates for TSAT were significantly higher in the FCM group at all visits; at week 2, 125 (69.8%) patients receiving FCM responded compared with 32 (36.0%) patients receiving FeSulf (p < 0.0001). Corresponding rates at 12 weeks were 139 (77.7%) for FCM and 59 (66.3%) for FeSulf (p < 0.05). Only one patient (in the FCM group) had a transfusion to replace intra-operative blood loss.

Fig. 2: Mean (SD) hemoglobin levels (g/l) by visit in patients with post-partum anemia (per protocol population, n = 268) [3]. Ferric carboxymaltose, at a maximum dose of 1000 mg iron over 15 min (15 mg iron/kg body weight, if body weight <66 kg) on day 1, with subsequent doses at 1-week intervals until each patient's calculated total iron requirement was reached (up to 3 weekly infusions), or oral ferrous sulfate, 100 mg, twice daily, for 12 weeks. Reproduced from Breymann et al. 2008 [3]. Reprinted with permission from the International Federation of Gynecology and Obstetrics (FIGO): Breymann C, Gliga F, Bejenaru C, Strizhova N. Comparative efficacy and safety of Intravenous ferric carboxymaltose in the treatment of postpartum iron deficiency anemia. Int J Gynaecol Obstet. 2008;101:67—73.

Compliance with oral therapy was encouraged and monitored (unlike the "real-life" situation), and was very high (>90%), but iron stores were nonetheless not replenished. Therefore, patients with more severe PPA might be at a higher risk of IDA once menstruation restarts. The iron deficit could also be carried forward to subsequent pregnancies.

A further superiority clinical trial, undertaken by Seid et al. [4], has also examined the efficacy, safety, and tolerability of i.v. FCM, compared with oral FeSulf in 291 women ≤10 days post-partum (mean Hb ≤10.0 g/dl on two or more laboratory tests) (Table 1). Women (aged 16—43 years) were randomized (1:1) to receive FCM (n = 143) ≤1000 mg iron over ≤15 min. repeated weekly to a calculated replacement dose (maximum 2500 mg) or FeSulf (n = 148) 325 mg (65 mg iron), orally, t.i.d., for 6 weeks. The primary efficacy endpoint was the percentage of patients achieving Hb >12.0 g/dl between baseline and end of study. Exclusion criteria included: myelosuppressive therapy or asthma therapy and recent blood transfusions or erythropoietin therapy within the 3 months prior to screening. Study withdrawal was required if the patient needed an intervention (i.e., ESA, blood transfusion, or i.v. or oral iron outside the study protocol). Patients were also stratified according to average baseline Hb levels (≤8.0 g/dl, 8.1—9.0 g/dl, or 9.1—10.0 g/dl), requirement for caesarean, and screening ferritin levels (≤25 or >25 µg/l).

It was assumed that success rates for the FeSulf group and the FCM group were 70% and 80%, respectively, and the alpha level for the two-sided Fisher's exact test was 0.05. Accordingly, approximately 320 randomized patients would provide 300 patients for the modified ITT population (the protocol-specified primary population for evaluating all efficacy endpoints, treatment administration/compliance and subject characteristics) and 270 patients for the evaluable population to achieve
Women with AUB are often untreated or inadequately treated for anemia [21]. AUB impacts women’s health-related QoL and puts a heavy economic burden on society [22].

A multicenter, open-label, randomized, Phase III study was undertaken to determine the efficacy and safety of rapid, large-dose i. v. FCM versus oral FeSulf in women with IDA secondary to AUB [6]. Two-hundred and thirty women (aged 18 years or older) with IDA (defined as Hb ≤11.0 g/dl, TSAT ≤25%, serum ferritin ≤100 μg/l) and AUB received FCM at a dose calculated to correct anemia and replenish iron stores (≤1000 mg iron over 15 min, repeated weekly to achieve a total calculated replacement dose); 226 women received FeSulf, 325 mg (65 mg elemental iron), t.i.d., for 6 weeks. Exclusion criteria included: red blood cell transfusion or parenteral iron administration within the prior 8 weeks, or an anticipated need for blood transfusion during the study; use of ESAs within the prior 12 weeks; initiation of hormonal therapy potentially affecting uterine bleeding in the 8 weeks before study entry; endometrial hyperplasia, and chronic viral infection. Randomization was stratified by Hb level (≤8.0, 8.1–9.5, or 9.6–11.0 g/dl) and by degree of uterine bleeding during the previous 28 days (mild/moderate, severe, or very severe) and the presence or absence of a poor response to prior oral iron therapy. According to statistical power and sample size calculations and using a two-sided Fisher’s exact test and 5% significance level, it was estimated that the study would have at least an 85% power to detect a 25% i. v. FCM treatment effect in comparison with oral FeSulf if at least 390 patients were enrolled [6].

Patients assigned to either group showed a similar severity of IDA at baseline (Hb, 9.4 g/dl in both groups; TSAT, 5.8% versus 5.6%; serum ferritin, 6.9 μg/l versus 6.8 μg/l, in the i. v. FCM and FeSulf groups, respectively). The primary efficacy endpoint was an increase in Hb ≥2.0 g/dl after initial treatment. Patients assigned to i. v. FCM were more likely to achieve an Hb rise ≥2.0 g/dl during the 42 days after baseline, than those receiving FeSulf (82% versus 62%, respectively; p <0.001).

Other secondary efficacy endpoints included an increase in Hb ≥3.0 g/dl or an Hb level ≥12.0 g/dl, mean Hb increase, safety assessment, and QoL scores. Patients assigned to i. v. FCM were more likely than those receiving FeSulf to achieve an Hb rise ≥3.0 g/dl (53% versus 36%; p <0.001 from baseline) or correction of anemia (an Hb rise to ≥12.0 g/dl [73% versus 50%; p <0.001 from baseline]). Patients treated with i. v. FCM achieved a greater mean Hb increase (3.3 versus 2.6 g/dl; p <0.001) and reported greater improvement in analog fatigue scales and SF-36 QoL scores (p <0.05 at day 14 and later) than those receiving FeSulf. There were no hypotensive or serious adverse drug events (ADEs) in either treatment group. Study ADEs were defined as all AEs that were possibly or probably related to treatment.
to study drug, as determined by the investigators. No deaths occurred during the study. There was no difference between groups in the number of infections reported and no infection was thought to be related to study drug. Discontinuation of study drug due to AEs occurred in five patients in the FCM arm and seven patients in the FeSulf arm. Patients assigned to oral iron therapy were more likely to experience GI ADEs, particularly constipation (14.2% versus 3.0%) and nausea (11.9% versus 3.5%). Those assigned to FCM were more likely to report headache (6.5% versus 4.4%) and transient fatigue (2.2% versus 0%). Transient, asymptomatic hypophosphatemia was also observed after FCM administration; this resolved spontaneously without specific treatment.

A potential limitation of this open-label trial is that patient-reported outcomes may have been affected by awareness of treatment assignment. This is particularly relevant of an i.v. versus an oral trial. However, health-related QoL scores tend to increase with Hb level, regardless of treatment [23], and treatment-related improvement in fatigue, specifically that seen in open-label interventional trials, is also seen in trials in which patients are masked to treatment assignment [24].

Patients who received FCM showed more rapid correction of iron depletion, iron-deficient erythropoiesis and anemia; greater improvement in health-related QoL scores tend to increase with Hb level, regardless of treatment [23], and treatment-related improvement in fatigue, specifically that seen in open-label interventional trials, is also seen in trials in which patients are masked to treatment assignment [24].

5. FCM in patients with CHF [9]

In patients with CHF, anemia is an independent risk factor for hospital admission and mortality, and has been shown to worsen as the severity of the CHF progresses [25, 26]. Beyond anemia, iron deficiency is becoming recognized as an important factor in CHF, which can mimic the symptoms of CHF and impact negatively on functional capacity and perceptions of health [27, 28]. Conversely, it is possible that iron repletion in iron-deficient patients with CHF may improve symptoms as it has been shown to improve symptomatic and exercise performance in patients without heart failure [29, 30].

A recent study of iron repletion in patients with CHF (Ferinject® Assessment in patients with IRon deficiency and chronic Heart Failure [FAIR-HF]) demonstrated that FCM can have a positive impact on functional symptoms (measured using the New York Heart Association [NYHA] class), patients' perceptions of their own health, and exercise capacity (six-minute walk test) [9]. FAIR-HF was a randomized, double-blind, placebo-controlled trial of 200 mg of iron as FCM administered weekly until patients were iron replete per the Ganzoni formula, then every four weeks [31]. After 24 weeks, 50% of patients (147/292) reported themselves to be much or moderately improved compared with baseline, significantly more than in the placebo group (28% [41/149]; odds ratio for improvement: 2.51 [95% confidence intervals: 1.75, 3.61]; p<0.001). Likewise, the improvement in NYHA class was significantly better in the FCM group than the placebo group (odds ratio for a one-NYHA-class improvement was 2.40 [95% confidence intervals: 1.55, 3.71]; p<0.001). The impact of FCM on functional symptoms and quality of life was observed in patients regardless of the presence of anemia (defined as ≤12.0 g/dl hemoglobin), indicating a role for iron repletion beyond the management of anemia. Significant improvements (p<0.001) in quality of life, CHF symptoms and functional capacity were observed as early as study week 4 [9].

6. FCM in other therapy areas

An important limitation of the studies by Qunibi et al. [7] and Schaefer et al. [8], reported in the following section, is that they are currently only available in abstract form, therefore, only limited information is available in the public domain at this stage. As information regarding definitions, statistical analyses and limitations are not provided, the results should be interpreted accordingly.

6.1 FCM in patients with CKD and/or on HD with IDA [7, 8]

The management of patients with anemia and undergoing dialysis has improved with the availability of ESAs [32]. Patients undergoing dialysis and those with CKD often require iron treatment because of frequent blood loss and (thus iron) loss [33]. Anemia places a high burden on patients with CKD not on dialysis [32, 34]. For these patients, therapy consists of maintenance of iron stores during ESA treatment [35, 36]. The approval of safe and efficient i.v. iron preparations (such as Isofer) has improved the management of anemia in patients on HD and in those with CKD. FCM offers specific advantages to patients with NDD-CKD, as it offers the ability to deliver up to 1000 mg of iron in a single 15-min dose. It would be ideal to give 1000 mg of iron during a single clinic visit, but concerns regarding hypotension and other AEs have precluded this approach in the past with traditionally available i.v. iron preparations [7].

A multicenter, randomized, open-label, Phase III study was conducted by Qunibi et al. [7] to compare the efficacy and safety of large doses of i.v. FCM (maximum first dose of 1000 mg of iron with up to two additional doses of 500 mg iron, as determined by iron indices; (n = 147) administered over a short period of time (15 min) versus oral FeSulf (325 mg [65 mg iron], t.i.d., for 56 days; n = 103)) in patients with NDD-CKD...
with IDA. Patients were randomly assigned to receive i.v. FCM or oral FeSulf. Randomization was stratified by the use of ESA, degree of CKD and baseline Hb level. Inclusion criteria were glomerular filtration rate ≤ 45 ml/min/1.73 m², Hb ≤ 11.0 g/dl, TSAT ≤ 25% and serum ferritin ≤ 300 μg/l. ESA doses, if any, must have been stable for at least 8 weeks prior to administration of iron and remain so throughout the study. Major exclusion criteria included documented history of discontinuation of oral iron therapy due to GI distress and i.v. iron use during the 12 weeks prior to the study start. The primary efficacy endpoint was the percentage of patients achieving an increase in Hb ≥ 1.0 g/dl at any time point between baseline and the end of the study or the time of intervention.

Baseline characteristics, Hb, iron parameters, and mean iron deficit at baseline were similar in both groups. Mean compliance with the prescribed oral iron regimen was 95.8% (unlike the "real-life" situation). The primary efficacy endpoint, the proportion of patients achieving an Hb increase ≥ 1 g/dl, was significantly greater in the i.v. FCM group than in the FeSulf group (60.4% [87/144] versus 34.7% [35/101]; p < 0.001).

Other efficacy endpoints included the percentage of patients achieving ≥ 1 g/dl increase in Hb by day 28; mean change to highest Hb; mean increase in Hb by day 42 and day 56; mean TSAT (%) and serum ferritin. FCM was also shown to be more efficacious than oral FeSulf across all ranked secondary endpoints. In patients receiving FCM, the percentage of patients achieving a ≥ 1 g/dl increase in Hb by day 28, the mean change to highest Hb (1.3 versus 0.8 g/dl, respectively; p < 0.001), and the mean increase in Hb by day 42 (1.0 versus 0.5 g/dl, respectively; p < 0.005) and 56 (1.0 versus 0.7 g/dl, respectively; p < 0.034) were all higher compared with patients receiving FeSulf. In patients with CKD not on dialysis, FCM (1000 mg iron over 15 min, with one or two additional 500 mg iron doses) was more effective than oral FeSulf therapy.

A multicenter, open-label, randomized, parallel group Phase III study was conducted in 183 (PP population) adult patients (aged 18—80 years) undergoing HD or haemofiltration with IDA (defined as Hb ≤ 11.5 g/dl; TSAT < 20%; or serum ferritin < 200 μg/l) secondary to CKD [8]. Patients received either 200 mg iron as FCM (n = 97, ITT population) given without dilution as a bolus-push injection or as ISC (n = 86, ITT population) given over 10 min. Both treatments were administered into the HD venous line, 1 h after the start of each dialysis session, two-to-three times weekly, until the total cumulative dose for each patient was reached. The maximum treatment period was 4 weeks and patients were followed for an additional 4 weeks. Patients were prescribed an ESA at baseline and must have received this treatment for at least 8 weeks prior to inclusion in the study. The ESA dose may have been decreased during the study, but no ESA dose increases were permitted during the study period.

The primary response was defined as the percentage of patients reaching an Hb increase of at least 1.0 g/dl at 4 weeks post-baseline. The primary response was met by 46.4% (45/97) and 37.2% (32/86) of patients in the FCM and ISC groups, respectively. Other efficacy endpoints included mean Hb levels during follow-up and serum ferritin levels. Mean Hb levels increased at the follow-up visit in both treatment groups: from 9.3 g/dl to 10.6 g/dl and from 9.3 g/dl to 10.3 g/dl in the FCM and ISC groups, respectively. Mean serum ferritin levels increased from baseline to week 2: from 90.4 μg/l to 723.4 μg/l and from 93.1 μg/l to 549.6 μg/l in patients treated with FCM and ISC, respectively (Fig. 4) [8]. At the end of follow-up, mean serum ferritin values were 465.3 μg/l versus 397.7 μg/l for the FCM and ISC groups, respectively. As increased doses of ESA were not permitted during this randomized, controlled study, biases that may be introduced due to uncontrollable influences of Hb level are presumed to affect both groups equally, thus, the increase in Hb can be solely attributed to efficient iron utilization. There was a trend towards better response for most efficacy parameters for patients with IDA undergoing HD allocated to FCM administered by push injection compared with ISC given over 10 min. The choice of an open design without blinding and the lack of a placebo arm were the main limitations of this study. An open design was necessary because of the differences in administration of the two study drugs;
that is, injection of ISC over 10 min. or a faster and simpler bolus-push injection of FCM. However, as efficacy was assessed by monitoring changes in laboratory parameters, it is unlikely that an open-label design could introduce bias to these results.

In addition to these Phase III studies, a Phase II, multicenter, open-label, single-arm study in 163 patients undergoing maintenance HD demonstrated that FCM was well tolerated and effective in the correction of Hb levels in patients with IDA [37].

7. Overall safety of FCM

Safety data are available from ten multiple-dose studies [38]: one Phase I/II pharmacodynamic study [39], one Phase III IBD study [2], two HD studies (one Phase II [37] and one Phase III [8]), three Phase III post-partum studies [3–5], one Phase III AUB study [6], and two Phase III NDD-CKD studies [7], one of which is long term. Safety evaluations included AE reporting, routine safety laboratory tests (clinical chemistry and hematology), vital signs (blood pressure, heart rate and body temperature) and physical examinations. Only three studies [2, 3, 8] included assessment of 12-lead electrocardiograms. In these studies [2–4], laboratory tests included urinalysis, and the study by Kulnigg and colleagues [2] also included markers of inflammation. The recording of AEs was based on spontaneous reports by the patients and observations by the study physician. AEs were defined along with categorization according to intensity, seriousness, and causality.

7.1 Ten multiple dose Phase I–III studies: safety data

Safety data were combined and analyzed from ten multicenter, Phase I–III FCM clinical trials involving approximately 3000 patients with IDA secondary to a variety of conditions (Table 2) [38]. The majority of studies compared FCM with oral iron (ferrous sulfate, 325 mg [65 mg iron], t.i.d.). One study compared FCM with ISC [8] and one study utilized a placebo-controlled crossover design in which all patients received both FCM and placebo [10].

Of those patients receiving FCM (n = 1968), 93% completed the study and approximately 88% (n = 1736) received a repletion dose of ≥1000 mg iron. The discontinuation rate due to any AE was similar in both groups (FCM group 1.5%; oral iron group 1.8%). No serious or life-threatening hypersensitivity (anaphylactoid) ADEs were reported with FCM. The most common ADE with FCM was headache (Table 3) [38]. Two non-serious hypersensitivity ADEs (0.1%) were reported with no changes in vital signs. No symptomatic hypotension occurred. Mild-to-moderate transient skin changes (rashes, urticaria and itching) were observed. A decrease in serum phosphorus was observed; the decreases were transient and asymptomatic (Table 3). The overall ADE rate was lower for the FCM group (302/1968 patients; 15.3%) compared with the oral iron group (218/834 patients; 26.1%)

<table>
<thead>
<tr>
<th>Population</th>
<th>FCM</th>
<th>Maximum single dose of iron as FCM (mg)</th>
<th>Oral iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDD-CKD</td>
<td>176</td>
<td>1000</td>
<td>103</td>
</tr>
<tr>
<td>HD-CKD</td>
<td>300</td>
<td>200</td>
<td>NA</td>
</tr>
<tr>
<td>IBD</td>
<td>201</td>
<td>1000</td>
<td>63</td>
</tr>
<tr>
<td>AUB</td>
<td>352</td>
<td>1000</td>
<td>226</td>
</tr>
<tr>
<td>PPA</td>
<td>700</td>
<td>1000</td>
<td>442</td>
</tr>
<tr>
<td>Other IDA</td>
<td>239</td>
<td>1000</td>
<td>NA</td>
</tr>
</tbody>
</table>

FCM, ferric carboxymaltose; HD-CKD, hemodialysis-dependent chronic kidney disease; AUB, abnormal uterine bleeding; IBD, inflammatory bowel disease; IDA, iron-deficiency anemia; ISC, iron sucrose; NDD-CKD, non-dialysis-dependent chronic kidney disease; PPA, post-partum anemia.


| Table 3: Drug-related adverse events (AEs) in patients taking ferric carboxymaltose (FCM) and oral iron according to the analysis of ten, multicenter, Phase I–III FCM clinical trials [38].

<table>
<thead>
<tr>
<th>ESRD Patients, n (%)</th>
<th>FCM (n = 1968)</th>
<th>Oral iron (n = 834)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One or more drug-related AE</td>
<td>302 (15.3)</td>
<td>218 (26.1)</td>
</tr>
<tr>
<td>Drug-related AEs at &lt;2% incidence</td>
<td>50 (2.5)</td>
<td>18 (2.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>33 (1.7)</td>
<td>48 (5.8)</td>
</tr>
<tr>
<td>Local injection-site reactions</td>
<td>31 (1.6)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased serum phosphorus</td>
<td>30 (1.5)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>21 (1.1)</td>
<td>22 (2.6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>20 (1.0)</td>
<td>5 (0.6)</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>19 (1.0)</td>
<td>9 (1.1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>17 (0.9)</td>
<td>94 (11.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (0.5)</td>
<td>23 (2.8)</td>
</tr>
<tr>
<td>Abdominal pain (upper)</td>
<td>7 (0.4)</td>
<td>10 (1.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (0.3)</td>
<td>12 (1.4)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>6 (0.7)</td>
</tr>
<tr>
<td>Feces discolored</td>
<td>0</td>
<td>11 (1.3)</td>
</tr>
</tbody>
</table>

Categorization of incidence refers to the FCM group.


| Table 4: Drug-related adverse events (AEs) in patients undergoing hemodialysis taking ferric carboxymaltose (FCM) and iron sucrose (ISC) [38].

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>FCM (n = 1968)</th>
<th>ISC (n = 118)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One or more drug-related AE</td>
<td>6 (3.0)</td>
<td>12 (10.2)</td>
</tr>
<tr>
<td>Drug-related AEs at ≥1% incidence</td>
<td>1 (0.8)</td>
<td>5 (4.2)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>2 (1.7)</td>
</tr>
</tbody>
</table>

26.1%) (Table 3). In patients undergoing HD, FCM administration resulted in fewer overall ADEs as well as fewer cases of treatment-related hypotension than ISC (Table 4) [38].

7.2 Safety in IDA
Bailie et al. [10] undertook a randomized, cross-over, double-blind, single-dose study comparing the safety and tolerability of i.v. FCM or placebo in patients with IDA. Five-hundred and fifty-nine patients with IDA received a dose of either FCM (15 mg/kg, maximum 1000 mg) over 15 min or placebo on day 0. On day 7, patients received the other agent. Safety evaluations were performed on days 7 and 14. The primary endpoint was the incidence of treatment-emergent AEs (TEAEs) during each 7-day study period. During the first 24 h and during the 7-day treatment period, at least one TEAE was experienced by 15.0% and 29.3% of patients after FCM, and by 11.4% and 19.7% of patients after placebo, respectively. Most TEAEs were classified as Grade 1 (mild [did not interfere with the patient’s usual function]) or 2 (moderate [interfered to some extent with the patient’s usual function]). Six patients had Grade 3 (severe [interfered significantly with the patient’s usual function]) TEAEs after FCM and nine patients after placebo. One patient had a Grade 4 (life-threatening [resulted in a threat to life or in an incapacitating disability]) TEAE of intestinal obstruction after FCM, and one patient had a Grade 5 TEAE of Aeromonas pneumonia and died 27 days post-FCM administration, but one patient had a Grade 5 TEAE of Aeromonas pneumonia and died 27 days post-FCM administration, but no significant AEs were noted in patients receiving placebo. Of drug-related Grade 3 events, four patients received FCM and five received placebo. The authors concluded that administration of FCM (15 mg/kg, maximum of 1000 mg) over 15 min was well tolerated and associated with minimal risk of AEs in patients with IDA [10]. The favorable safety profile of FCM was further demonstrated in the two studies in patients with CHF plus iron deficiency and/or anemia [9, 40].

7.3 Safety in PPA
Breymann et al. [3] conducted an investigation of the safety and tolerability of i.v. FCM compared with oral FeSulf and measurement of levels of iron in breast milk from a subset of patients in the study of PPA. Overall, AEs (excluding those relating to IDA or to the therapeutic effect of iron treatment, e.g., ferritin increase) were experienced by 26.0% (59/227) of patients treated with FCM and by 22.2% (26/117) of patients treated with FeSulf (Fisher’s Exact test; p = 0.510) in the breast milk subset study (Table 5). Except for infusion-site burning, FCM was better tolerated than FeSulf. Statistically significant differences were seen in the following cases (FCM versus FeSulf): GI disorders (3.5% versus 10.3%; p = 0.015), general disorders and administration-site con-

tions (6.2% versus 0.0%; p = 0.003), and musculoskeletal and connective tissue disorders (0% versus 2.6%; p = 0.039). Constipation was less common in the FCM group (1 patient [0.4%] than in the FeSulf group (8 patients [6.8%]). In the FCM group, 2.2% of patients experienced infusion-site burning and 1.3% experienced infusion-site pain. Only 1.7% of patients in the control group experienced arthralgia. There were no safety concerns identified in breast-fed infants of mothers receiving FCM or FeSulf (Table 5).

A potential limitation of the pooled safety data for FCM and other i.v. iron treatments is that full assessment of the safety profiles of i.v. iron preparations is difficult to acquire. There may be significant inter-rater variability and possible subjectivity associated with the reporting of AEs by investigators across centers in a multicenter trial. Moreover, safety was assessed as a secondary endpoint in many of the trials. Clinical study designs are limited by exclusionary patient entry criteria, small numbers of exposed patients and short durations of treatment [41]. There are many examples of important AEs that were not detected in clinical trials with other medications, but that were only discovered during post-marketing surveillance [42]. Moreover, more serious idiosyncratic adverse reactions are rare, which makes case ascertainment difficult, even in large patient populations.
8. Conclusions

The efficacy and safety of FCM in correcting iron deficiency have been investigated in a wide range of indications in the nine Phase III clinical studies reported here. Results of the available studies have demonstrated that i. v. FCM can be administered at doses of up to 1000 mg iron during a minimum administration time of 15 min and is effective in the correction of iron deficiency across diverse patient populations (including IBD, PPA, AUB, CKD, HD and CHF), providing clear improvement in all indices of anemia (rapid Hb increase and rapid normalization of iron stores, as assessed by serum ferritin and TSAT). In addition, in two studies [6, 7], i. v. FCM has been shown to be superior to oral FeSulf in terms of the proportions of patients achieving "success" (in terms of Hb increase according to various definitions). In patients with IBD [2] or PPA [5], increases in Hb indicated a faster response to treatment with FCM than with oral FeSulf, while in patients with IDA secondary to CKD [8], FCM demonstrated a comparable efficacy to ISC in achieving an increase in Hb ≥ 1.0 g/dl at 4 weeks post-baseline, although there was a trend of more pronounced increases on most response parameters in patients with FCM and with low baseline Hb values compared with the ISC arm. In all Phase III studies, FCM treatment led to a rapid and significant rise in mean serum ferritin, which remained elevated for several weeks after the last infusion, indicating the utilization of stored iron during the weeks of hematopoiesis following the infusions.

Safety data from more than 3000 patients has shown that FCM is well tolerated with a low risk of immunogenicity. The incidence of AEs and the discontinuation rate due to AEs was lower in patients receiving FCM than in patients receiving oral iron or i. v. ISC (in HD). No safety concerns have been identified in breast-fed infants of mothers receiving FCM.

Overall, FCM is considered to be an optimal treatment for parenteral iron administration, providing a very efficient and convenient means of delivering iron in patients with IDA.

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Conflict of Interest

The author has received honoraria from Vifor Pharma and been a member of the Speakers' Bureau. He has previously obtained research funding from American Regent Inc. The author received no reimbursement for the development of this manuscript.

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Ferric Carboxymaltose


[37] Covic A, Mircescu G. Safety and efficacy of intravenous (i.v.) ferric carboxymaltose (FCM) in anaemia haemodialysis (HD) patients: a multicenter, open-label clinical study. Poster presented at the 42nd American Society of Nephrology, San Diego, CA; SA-P02419.


