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

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Abstract

OBJECTIVES: To compare the safety and efficacy of iron carboxymaltose with ferrous sulfate to treat iron deficiency anemia in the post partum. METHODS: Patients were randomized (2:1 ratio) to receive iron carboxymaltose (up to 3 weekly doses of 1000 mg maximum, applied in 15 min; n=227) or ferrous sulfate (100 mg twice daily, 12 weeks; n=117). Changes in hemoglobin and iron stores up to week 12 were analyzed. RESULTS: Iron carboxymaltose was as effective as oral iron sulfate in changing hemoglobin, despite the much shorter treatment period (2 weeks vs 12 weeks). Ferritin levels were significantly higher. Except for injection site burning, iron carboxymaltose was better tolerated than ferrous sulfate, mainly concerning gastrointestinal side effects. There were no safety concerns identified in breast-fed infants. CONCLUSION: Parenteral iron carboxymaltose is a safe and effective treatment option for postpartum anemia, with advantages of a shorter treatment period, better compliance, rapid normalization of iron storages, and lower incidence of gastrointestinal side effects.
Comparative efficacy and safety of intravenous ferric carboxymaltose in treatment of post-partum iron deficiency anemia.
Abstract

Objective
This study compared efficacy and safety of iron carboxymaltose, a novel intravenous iron, with ferrous sulfate in treating iron deficiency anemia in women post-partum.

Method
Patients were randomized (2:1 ratio) to iron carboxymaltose (up to 3 weekly doses of maximum 1000 mg applied in 15 minutes; n=227) or ferrous sulfate (100 mg bid, 12 weeks; n=117). Changes in hemoglobin and iron stores up to week 12 were analyzed.

Result
Iron carboxymaltose was as effective as oral iron sulfate in changing hemoglobin, despite the much shorter treatment period (2 weeks vs. 12 weeks). Ferritin levels were significantly higher. Except injection site burning, iron carboxymaltose was better tolerated than ferrous sulfate, mainly concerning gastrointestinal side effects. There were no safety concerns in breast-fed infants.

Conclusion
Parenteral iron carboxymaltose is a safe and effective treatment option for post-partum anemia, with advantages of a shorter treatment period, better compliance, rapid normalization of iron storages, and lower incidence of gastrointestinal side effects.

NOTE to Journal:
Abstract word count (limit 150 words): 154
Word count for body of text (Introduction to end Discussion) (limit 2600): 2615.
Total word count (including tables and references): 3613
This manuscript includes 3 tables and 3 figures.
Introduction

Iron deficiency anemia (IDA) is very common in women post partum. Oral treatment with ferrous sulfate has been considered the standard of care in post-partum IDA, but parenteral iron treatment is expected to be advantageous in cases when oral iron therapy is not tolerated due to gastrointestinal adverse effects, in patients with poor compliance or in patients with more severe anemia, where intravenous iron treatment ensures a fast response to iron treatment. As a result, there is increased interest in parenteral iron therapy, which can provide a greater and more rapid iron supply than oral iron supplementation.[1,2,3,4,5,6]

Recently, a new parenteral iron preparation, iron carboxymaltose, was developed to facilitate effective treatment of IDA as well as rapid replacement of iron stores. Iron carboxymaltose has a nearly neutral pH (5.0 to 7.0) and physiological osmolarity, which makes it possible to administer higher single doses over shorter time periods than other parenteral preparations.

This study was carried out in women with post partum IDA, who were expected to benefit from the short treatment period permitted by the larger doses that can be given parenterally than orally. The aims of the study were to assess the effects of iron carboxymaltose on hemoglobin (Hb) increase, iron status, and safety for both mother and breast-fed infant.

Material and Methods

A multi-center, open-label, randomized, controlled, parallel group phase III study in women with post-partum IDA (Hb ≤105 g/L). Patients with anemia other than anemia caused by blood loss secondary to delivery and iron deficiency were ineligible. All patients provided written informed consent. Patients were randomized according to a 2:1 ratio (iron carboxymaltose:ferrous sulfate) with stratification by country and severity of anemia. Patients received either an intravenous infusion of iron carboxymaltose (FERINJECT®, Vifor International, St. Gallen, Switzerland) at a maximum dose of 1000 mg iron (15 mg iron/kg body weight if body weight <66 kg; over 15 minutes) on Day 1, with subsequent doses at 1-week intervals until the patient’s calculated total iron requirement was reached (up to three weekly infusions), or oral ferrous sulfate (Plastufer, Valeant Pharmaceuticals International) 100 mg twice daily for 12 weeks. The patient’s total iron requirement was calculated using the modified formula of Ganzoni [7] and the iron carboxymaltose dose was adapted depending on body weight, ferritin and transferrin saturation.
(TfS) levels. All patients received first study medication within 7 days post-partum and then attended follow-up visits after 1, 2, 4 and 12 weeks (end of study). Twenty centers in three countries included patients, with patient participation between June 2004 and August 2005. The primary objective of this study was to evaluate the efficacy of intravenous iron carboxymaltose vs. oral ferrous sulfate in treating IDA in women with post-partum anemia. Secondary objectives included investigation of the safety and tolerability of iron carboxymaltose vs. oral ferrous sulfate, and measurement of levels of iron in breastmilk from a subset of patients. Efficacy was assessed by change from baseline to week 12 in Hb levels (primary endpoint); changes from baseline in ferritin and TfS; the number and proportions of patients (‘response rate’) who achieved Hb levels of 120 to 160 g/L, ferritin levels of 50 to 800 µg/L, and TfS levels of 20 to 50%; the number and proportion of patients who needed transfusions. Measurement of iron-status parameters, as well as Hb, was performed by a central laboratory. Safety was assessed by means of treatment-emergent adverse events in the mother and breast-fed infant, vital signs, electrocardiogram, physical examinations and clinical laboratory panels. The study was approved by the relevant Independent Ethics Committees. The planned sample size of 348 patients was based on a 90% power to detect non-inferiority using a margin of 5 g/L (half the estimated clinically relevant change in Hb), an $\alpha$ of 0.025 (1-sided), and expected standard deviation (SD) of 12 g/L, with a 20% dropout rate. The breastmilk substudy was performed at 2 sites in Romania, and the planned number of patients (10 in each group) was considered sufficient to gain insight into the effect of iron carboxymaltose on iron levels in breastmilk. Analyses of efficacy parameters were based on both the full analysis/intent-to-treat (ITT) set and the per-protocol (PP) set. For change in Hb from baseline to week 12, analysis was performed by calculating the two-sided 95% confidence interval (CI) for the difference “iron carboxymaltose minus ferrous sulfate” in Hb change, from an analysis of covariance (ANCOVA); non inferiority was concluded if the lower bound was $\geq$-5 g/L, and superiority if the lower bound was $\geq$0 g/L. Descriptive statistics (mean, SD, range) are presented for measured values and for absolute changes from baseline to all subsequent timepoints, including 95% CIs for changes from baseline. The same ANCOVA model as above was applied to continuous secondary efficacy endpoints to assess treatment differences. For response rates, number and proportion of patients were tabulated with the corresponding 95% CIs. A descriptive comparison of response rates between the two groups was performed by means of a 2-sided
chi-squared test, with a further exploratory analysis using the Cochran-Mantel Haenszel test with adjustment for severity of anemia, country and enrolment. Differences between groups in the number of patients experiencing adverse events by body system were tested using Fisher’s exact test. For all analyses, p-values <0.05 were considered statistically significant. Unless otherwise specified, efficacy results are from the PP analysis; the results for the ITT set were similar unless noted.

Results

From 824 patients screened, 349 were randomized (Figure 1). Main demographic and baseline characteristics are summarized in Table 1; no differences between the groups were detected. The most common method of delivery in both groups was vaginal. Cesarean section was more common in Poland 6/11 (54.5%) and Romania (976/145 [52.4%]) than in the Russian Federation (16/111 [14.4%]). Mean calculated iron deficit was similar between groups (1365.8 mg and 1393.7 mg, respectively); the majority of patients in the iron carboxymaltose group required only 1 or 2 infusions (mean total dose 1346.7 mg in the safety set). For breast-fed infants, no differences between groups for birth weight, head circumference, length or sex were detected. Mean compliance for ferrous sulfate capsules was >90% (by counts of returned unused capsules at the week 4 and 12 visits). Reasons for non-compliance included forgetting to take the tablets, taking 1 instead of 2 tablets, and losing or discarding the bottle. For iron carboxymaltose, compliance was 100%, with the exceptions of one patient with a compliance of 73% (the patient experienced an allergic rash after infusion) and one patient who received an incorrectly calculated dose.

Hemoglobin

Hb levels increased from baseline to week 12 in both groups (Figure 2), increasing to a mean of 130.4 g/L in the iron carboxymaltose group and 128.9 g/L in the ferrous sulfate (control) group (mean change from baseline 33.7 g/L and 32.9 g/L, respectively). There were no statistically significant differences between groups at any timepoint. Iron carboxymaltose was non-inferior to ferrous sulfate in terms of change in mean Hb from baseline to week 12. However, superiority could not be concluded because the lower limits of CIs were below zero at all time points analyzed (baseline to weeks 2, 4 and 12). An additional analysis evaluating only patients who had
baseline Hb $\leq 105$ g/L supported the validity of the main analysis. There were no statistically significant differences between groups for response rate at any timepoint (Table 2).

**Ferritin**

In the iron carboxymaltose group, mean ferritin levels increased from 39.9 µg/L at baseline to 568.2 µg/L at week 1 (Figure 3). A decrease was observed in the following weeks, but ferritin levels remained considerably above baseline at all visits (mean 161.2 µg/L at week 12). In contrast, patients in the control group showed only a marginal increase of ferritin levels (32.4 µg/L to 34.8 µg/L at week 2 and 43.3 µg/L at week 12). The change from baseline was significantly higher in the iron carboxymaltose group compared to the control group for all visits, including Week 12 ($p<0.0001$). Response rates for ferritin were also significantly higher in the iron carboxymaltose group than the control group at all timepoints (Table 2).

**Transferrin Saturation**

Mean values of TfS increased from baseline and remained $>20\%$ from week 2 to week 12 in both groups, reaching maximum mean values at week 4 (40.1% and 27.9%, respectively). Changes from baseline of mean TfS values were statistically significantly higher in the iron carboxymaltose group compared to the control group at all visits ($p \leq 0.0004$). Response rates for TfS were significantly higher in the iron carboxymaltose group at all visits (Table 2).

**Red Cell Indices**

No clinically relevant changes from baseline in mean corpuscular volume or mean corpuscular hemoglobin were detected (not analyzed statistically). There was an increase in mean reticulocyte counts in the iron carboxymaltose group only, from $71.0 \times 10^9$/L at baseline to $110.6 \times 10^9$/L at week 1, returning to $91.9 \times 10^9$/L at week 2 and $60.9 \times 10^9$/L at week 4. In the control group, mean reticulocyte counts showed no increase at any timepoint.

**Transfusions**

Only one patient (in the iron carboxymaltose group) had a transfusion to replace intraoperative blood loss (patient excluded from the PP set).
Iron carboxymaltose was well tolerated and treatment was not associated with any clinically relevant safety concerns. Overall, adverse events were experienced by 26.0% (59/227) of patients in the iron carboxymaltose group and by 22.2% (26/117) of patients in the control group (excluding adverse events relating to IDA or the therapeutic effect of iron treatment, eg, Hb decreased, ferritin increased) (Table 3). There was no statistically significant differences between the two groups in the overall adverse event profile (p=0.510). The body system with the highest incidence of events was ‘infections and infestations’ (nasopharyngitis and respiratory tract infection were the commonest events), with events in 8.4% and 3.4% of patients in the iron carboxymaltose and control groups, respectively, and no statistically significant differences between the groups (p=0.110). Statistically significant differences were seen in the following body systems (iron carboxymaltose vs. control): gastrointestinal disorders (3.5% vs. 10.3%; p=0.015), general disorders and administration site conditions (6.2% vs. 0%; p=0.003) and musculoskeletal and connective tissue disorders (0% vs. 2.6%; p=0.039). Constipation was less common in the iron carboxymaltose group (0.4% vs. 6.8%). Patients in the iron carboxymaltose group experienced infusion site burning (2.2%) and infusion site pain (1.3%). Only patients in the control group experienced arthralgia (1.7%).

Adverse reactions (adverse events considered possibly, probably or certainly related to study drug) were experienced by 10.6% and 11.1% of patients in the iron carboxymaltose and control groups, respectively. Two patients in the iron carboxymaltose group and none in the control group experienced severe adverse reactions; hepatic enzymes increased and hypersensitivity. There were no cases of anaphylactic shock/reaction. Adverse reactions leading to discontinuation were infusion site burning and panic attack (1 patient), and rash (1 patient) in the iron carboxymaltose group, and diarrhea (1 patient) in the control group. Two patients, both in the iron carboxymaltose group (0.9%), experienced serious adverse events (endometritis in one patient and sepsis after vaginal hysterectomy in the other patient); none of these events were considered drug-related.

There were no clinically relevant changes in vital signs or physical examinations during the study. Transient elevations in liver enzymes were observed in a minority of patients (see Table 3). Levels of ferritin and TfS indicating iron intoxication were not observed.
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**Breastmilk Substudy**

For 11 patients in the iron carboxymaltose group, mean iron in breastmilk increased from 0.500 mg iron/kg breastmilk at baseline to a maximum of 1.447 mg/kg 24 hours post-dose. Mean values decreased to 0.513 mg/kg week 1 pre-dose, increased to 0.615 mg/kg 1-3 hours post-dose at week 1 and were 0.991 mg/kg at week 2, pre-dose. For 14 patients in the control group, mean iron values in breastmilk decreased from 0.407 mg/kg at baseline to 0.332 mg/kg 48 hours post-dose. Mean values increased slightly over time up to 0.779 mg/kg at week 2, pre-dose. Mean iron breastmilk values were significantly higher in the iron carboxymaltose group at 48 hours after the first dose (+0.101 mg/kg versus -0.075 mg/kg, respectively; p=0.0052).

**Tolerability in Breast-fed Infants**

Adverse events in breast-fed infants are summarized in Table 3. The low frequency of adverse events in both groups was too small to draw any meaningful conclusion. However, there was no evidence of adverse effects of iron carboxymaltose on breast-fed infants.

**Discussion**

In this study, parenteral and oral iron treatment were both effective in treating post-partum IDA over 12 weeks. Based on the primary efficacy variable (Hb increase at week 12), iron carboxymaltose was non-inferior to ferrous sulfate, and the similarity of results in the PP and ITT sets supports the robustness of the results. Thus, parenteral iron carboxymaltose is as effective as oral ferrous sulfate in treating post-partum IDA despite the much shorter treatment period, and a lower total dose of iron (mean 1346.7 mg versus 16.8 g), highlighting the efficient utilization of parenteral iron.

In the iron carboxymaltose group, increases in ferritin and TfS were significantly greater than in the ferrous sulfate group at all timepoints, demonstrating a successful increase in iron storage and availability for erythropoiesis. The decrease in ferritin after week 2 in the iron carboxymaltose group indicates utilization of stored iron during the weeks of increased hematopoiesis, as supported by the increase in reticulocyte counts. This increase in iron stores is a significant benefit over oral iron, which does not replenish iron stores in patients with IDA. Further, these results indicate that iron carboxymaltose may be advantageous in patients with severe anemia,
including those receiving rHuEpo treatment, where rapid availability of iron is important.[3,8,9,10,11,12,13,14]

In the substudy of iron in breastmilk, mean iron values increased from baseline to week 2, pre-dose, in both groups. The iron breastmilk values were significantly higher in the iron carboxymaltose group at 48 hours after the first dose. However, the small number of patients included in the substudy and the high degree of inter-individual variation makes treatment group comparisons inconclusive.

Iron carboxymaltose was well tolerated by patients with post-partum IDA at 1 to 3 single doses. The overall adverse event profile was similar between groups, and there were no treatment-related serious adverse events. The significantly higher frequency of gastrointestinal disorders in the ferrous sulfate group supports the findings of other studies, that oral iron medications are known to cause gastrointestinal side effects.[15,16] Even in this study, where compliance to oral therapy was encouraged and monitored (unlike the ‘real-life’ situation), and was very high (>90%), iron stores were not replenished. This is of particular concern in patients with more severe IDA, as they are at higher risk of recurrent IDA once menstruation restarts, and the iron deficit could be carried forward into subsequent pregnancies. Iron carboxymaltose also has several advantages over other parenteral iron preparations. It does not contain dextran and does not react with dextran antibodies, and thus there is no risk of anaphylactic reactions of the type seen with iron dextran.[17] In addition, iron carboxymaltose has positive characteristics compared to iron sucrose (Venofer®), which include a lower pH, lower osmolarity, and higher single dose administration.[18] Due to its safety profile, it can be given over a short-term period in in-patient or out-patient facilities.

In conclusion, iron carboxymaltose is a safe and effective treatment option for patients with post-partum IDA, and no evidence of risk to their breast-fed infants. Iron carboxymaltose has advantages over oral ferrous sulfate of a shorter treatment period, ensured compliance, no gastrointestinal side effects, and replacement of iron stores. Thus, iron carboxymaltose should be ideally suited for treatment of patients with IDA who cannot tolerate oral iron supplementation, or in patients requiring rapid replenishment of iron stores.
Acknowledgments

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References


Table 1  Demographic and Baseline Characteristics: Safety (N=344), PP Sets (N=268)

<table>
<thead>
<tr>
<th>Demographic characteristic</th>
<th>Iron Carboxymaltose Safety (N=227)</th>
<th>PP (N=179)</th>
<th>Ferrous Sulfate Safety (N=117)</th>
<th>PP (N=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
<td>27.7 (5.5)</td>
<td>27.8 (5.4)</td>
<td>27.5 (5.4)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>18 - 44</td>
<td>18 - 44</td>
<td>19 – 41</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>Mean (SD)</td>
<td>22.70 (4.24)</td>
<td>22.78 (4.31)</td>
<td>22.35 (3.33)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>16.3 - 42.7</td>
<td>16.3 - 42.7</td>
<td>14.7 - 32.9</td>
</tr>
<tr>
<td>Delivery Method, N (%)</td>
<td>Vaginal</td>
<td>145 (64.2)</td>
<td>113 (63.5)</td>
<td>71 (60.7)</td>
</tr>
<tr>
<td></td>
<td>Cesarean section</td>
<td>80 (35.4)</td>
<td>65 (36.5)</td>
<td>42 (35.9)</td>
</tr>
<tr>
<td></td>
<td>Forceps</td>
<td>-</td>
<td>-</td>
<td>4 (3.4)</td>
</tr>
<tr>
<td></td>
<td>Vacuum</td>
<td>1 (0.4)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hemoglobin (g/L) *</td>
<td>Mean (SD)</td>
<td>96.6 (14.6)</td>
<td>96.7 (14.7)</td>
<td>97.6 (15.8)</td>
</tr>
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<td></td>
<td>Range</td>
<td>52 - 145</td>
<td>52 - 145</td>
<td>62 – 173</td>
</tr>
<tr>
<td>Ferritin (µg/L) *</td>
<td>Mean (SD)</td>
<td>45.5 (110.9)</td>
<td>39.9 (63.7)</td>
<td>33.4 (27.7)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>2 - 1392</td>
<td>2 - 605</td>
<td>0 – 218</td>
</tr>
<tr>
<td>Transferrin Saturation (%) *</td>
<td>Mean (SD)</td>
<td>12.1 (9.9)</td>
<td>11.7 (8.8)</td>
<td>12.8 (9.5)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>2 - 74</td>
<td>2 - 54</td>
<td>2 – 51</td>
</tr>
<tr>
<td>Calculated Iron Deficit (mg)</td>
<td>Mean (SD)</td>
<td>1363.1 (181.9)</td>
<td>1365.8 (179.7)</td>
<td>1383.5 (186.0)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>720 - 2024</td>
<td>720 - 2024</td>
<td>829 – 2062</td>
</tr>
</tbody>
</table>

* Last measurement prior to first study drug administration.
Not analyzed statistically for treatment group differences.
Abbreviations: SD: standard deviation.
### Table 2: Response Rates for Hemoglobin, Ferritin and Transferrin Saturation: PP Set (N=268)

<table>
<thead>
<tr>
<th>Efficacy Parameter (Target Values)</th>
<th>Response Rate</th>
<th>Iron carboxymaltose</th>
<th>Ferrous sulfate</th>
<th>p-values *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>95% CI</td>
<td>N (%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Hemoglobin (120-160 g/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>95 (53.1)</td>
<td>45.8 - 60.2</td>
<td>42 (47.2)</td>
<td>37.2 - 57.5</td>
</tr>
<tr>
<td>Week 4</td>
<td>140 (78.2)</td>
<td>71.6 - 83.6</td>
<td>63 (70.8)</td>
<td>60.6 - 79.2</td>
</tr>
<tr>
<td>Week 12</td>
<td>152 (84.9)</td>
<td>78.9 - 89.4</td>
<td>73 (82.0)</td>
<td>72.8 - 88.6</td>
</tr>
<tr>
<td>Ferritin (50-800 µg/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>127 (70.9)</td>
<td>63.9 - 77.1</td>
<td>12 (13.5)</td>
<td>7.9 - 22.1</td>
</tr>
<tr>
<td>Week 4</td>
<td>150 (83.8)</td>
<td>77.7 - 88.5</td>
<td>15 (16.9)</td>
<td>10.5 - 26.00</td>
</tr>
<tr>
<td>Week 12</td>
<td>139 (77.7)</td>
<td>71.0 - 83.1</td>
<td>29 (32.6)</td>
<td>23.7 - 42.9</td>
</tr>
<tr>
<td>Transferrin saturation (20-50%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>125 (69.8)</td>
<td>62.7 - 76.1</td>
<td>32 (36.0)</td>
<td>26.8 - 46.3</td>
</tr>
<tr>
<td>Week 4</td>
<td>130 (72.6)</td>
<td>65.7 - 78.6</td>
<td>45 (50.6)</td>
<td>40.4 - 60.7</td>
</tr>
<tr>
<td>Week 12</td>
<td>139 (77.7)</td>
<td>71.0 - 83.1</td>
<td>59 (66.3)</td>
<td>56.0 - 75.3</td>
</tr>
</tbody>
</table>

* Statistical tests: Chi-squared test or Cochran-Mantel-Haenszel test with stratification adjustment for severity of anemia, country and enrolment.

Abbreviations: CI: confidence interval, NS: non significant.
<table>
<thead>
<tr>
<th>Adverse events in mothers *</th>
<th>Iron carboxymaltose (N=227)</th>
<th>Ferrous Sulfate (N=117)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>At least one adverse event</td>
<td>59 (26.0)</td>
<td>26 (22.2)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>7 (3.1)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (0.4)</td>
<td>8 (6.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (2.6)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>5 (2.2)</td>
<td>3 (2.6)</td>
</tr>
<tr>
<td>Infusion site burning</td>
<td>5 (2.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>C-reactive protein increased</td>
<td>4 (1.8)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Uterine hemorrhage</td>
<td>3 (1.3)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Changes in liver function tests **</td>
<td>8 (3.5)</td>
<td>3 (2.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse events in breast-fed infants * (N=229)</th>
<th>Ferrous Sulfate (N=117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one adverse event</td>
<td>24 (10.5)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Erythema</td>
<td>5 (2.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

* Event terms reported in 4 or more mothers or in 3 or more breast-fed infants in total, in descending order of frequency.
** Reported as: elevated aspartate aminotransferase, and/or alanine aminotransferase, bilirubin or gamma-glutamyl transpeptidase
Figure 1

Assessed for eligibility (n= 824)

Excluded (n= 475) (Mostly patients with insufficient anemia)

Enrollment Randomization (n= 349)

Iron Carboxymaltose
Received treatment (at least one dose) (n= 227)
Did not receive allocated treatment or had no efficacy data available (n= 4)

Discontinued prematurely:
- Adverse event (n= 3)
- Consent withdrawal (n= 13)
- Lost to follow-up (n= 7)
- Non-compliance (n= 6)

Analyzed safety & ITT (n= 227)
Analyzed PP (n= 179)
Excluded from PP analysis (n= 48)
- Major protocol deviation (n= 19)
- Premature discontinuation (n= 29)

Ferrous Sulfate
Received treatment (at least one dose) (n= 117)
Did not receive allocated treatment or had no efficacy data available (n= 1)

Discontinued prematurely:
- Adverse event (n= 1)
- Consent withdrawal (n= 7)
- Lost to follow-up (n= 3)
- Non-compliance (n= 4)

Analysis
Safety set (n= 344)
ITT set (n= 344)
PP set (n= 268)

Allocation

Follow-Up

Enrollment Randomization (n= 349)
Figure 2

![Graph showing changes in Hemoglobin (g/L) levels across different visits and interventions. The graph includes line graphs for different substances and their corresponding levels at various time points.]

- Visit: Screening 1, Screening 2, Screening 3, Baseline, Week 1, Week 2, Week 4, Week 12.
- Substances: Iron, Carboxy, Maltose, Ferrous Sulfate.
- Hemoglobin levels range from 70 to 150 g/L.
Figure 3
Figure Titles and Legends

Figure 1: Disposition of Patients.
Abbreviations: PP: Per-protocol, ITT: Intent-to-treat.

Figure 2: Mean ± Standard Deviation Hemoglobin Levels (g/L) by Visit – Per Protocol Population (N=268).

Figure 3: Mean ± Standard Deviation Ferritin Levels (µg/L) by Visit – Per Protocol Population (N=268)