2. SYNOPSIS

IDNA 2009-01

Name of Company:	Vifor Pharma Ltd.
Name of Finished Product:	Ferinject®
Name of Active Ingredient(s):	Ferric carboxymaltose

Report Date:	10 May 2012
Title:	A Multicentre Randomised Placebo-controlled Study to Assess the Efficacy and Safety of a Single Administration of Ferric Carboxymaltose (1,000 mg Iron) in Improving Fatigue Symptoms in Iron-deficient Non-anaemic Women of Child Bearing Age
Short Title:	Effect of ferric carboxymaltose in improving fatigue in iron-deficient non-anaemic women: the PREFER study
Indication:	Iron deficiency
Phase:	4
Study Code:	IDNA 2009-01
Co-ordinating Investigator:	Dr. Bernard Favrat
Study Centre(s):	21 sites in 4 European countries (Austria, Germany, Sweden and Switzerland)
Objectives:	Primary Objective: • To assess the efficacy of a single intravenous (IV) administration of ferric carboxymaltose (FCM) (1,000 mg iron) compared with placebo in improving fatigue symptoms in iron-deficient non-anaemic (IDNA) women of child bearing age. Secondary Objective(s): • To compare the efficacy of a single IV application of FCM with that of placebo on change of iron status on Day 56 (i.e., proportion of subjects with haemoglobin (Hb) ≥120 g/L; serum ferritin (s-ferritin) ≥50 mcg/L; transferrin saturation (TSAT) >20%). • To determine the relationship between change in iron status (s-ferritin and TSAT) and improvement of fatigue symptoms. • To compare the efficacy of a single IV administration of FCM with that of placebo in improving cognitive function (attention, concentration and short-term memory). • To assess the safety of single IV administration of FCM.
Design:	Multicentre, randomised, placebo-controlled, single-blinded, parallel group, comparative superiority study.

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Treatment:	Active: FCM (Ferinject), 1 single IV application of 1,000 mg of iron. Batch No.: 910210. Placebo: 1 single administration of 250 mL of sterile 0.9% sodium chloride solution for IV infusions. Batch No.: 9404E43.
Inclusion Criteria:	1. Signed informed consent prior to study specific procedures. 2. Premenopausal, regularly menstruating women. 3. Age ≥18 years. 4. Body weight (BW) between 50 and 90 kg. 5. Hb ≥115 g/L. 6. Iron deficiency at screening defined as follows: – s-ferritin level <50 mcg/L, AND, TSAT <20%, OR, – s-ferritin level <15 mcg/L. 7. Serum C-reactive protein: – <5 mg/L if not on oral contraception, OR, – <20 mg/L if use of oral contraception. 8. Minimum total score of 5 on the Piper Fatigue Scale (PFS) (mean of items 2 to 23). 9. Negative pregnancy test (serum human chorionic gonadotropin (hCG) at screening). 10. Normal levels of Vitamin B_{12} and folic acid at screening. 11. Adequate contraception during the study period and for 1 month following study completion. 12. Availability and willingness to complete all study visits and procedures per protocol.
Exclusion Criteria:	1. Hb level <115 g/L. 2. Haemoglobinopathy. 3. Haemochromatose. 4. Major depressive disorder based on PHQ-9 (5 items with scores ≥2; 1 of which corresponds to question number 1 or 2). 5. Any active or unstable concurrent medical condition (e.g., cancer, renal dysfunction, liver dysfunction (aspartate aminotransferase; alanine aminotransferase >3-fold upper limit), angina (Class IV)).

Exclusion Criteria: (Cont'd)	6. Known human immunodeficiency virus/acquired immunodeficiency syndrome, hepatitis B virus or hepatitis C virus infection. 7. Chronic inflammatory disease (e.g., rheumatoid arthritis; inflammatory bowel disease). 8. Documented history of clinically significant level of sleep apnoea defined as 5 or more episodes per hour of any type of apnoea. 9. Intake of concurrent medications that could interfere with physical or mental performance (e.g., antidepressant, antihistamines, narcotic or any chemotherapeutic agents known to cause drowsiness). 10. Important recent weight loss (>10% within the past month). 11. BW <50 kg or >90 kg. 12. Thyroid dysfunction, thyroid stimulating hormone >4 µU/mL. 13. Intake of iron preparations 4 weeks prior to screening. 14. Use of gestagens e.g., Implanon®, Mirena®, Depo-Provera® for menstruation repression. 15. Known hypersensitivity to FCM or to any other iron preparation. 16. Pregnancy (positive hCG test at screening) or breast feeding. 17. Participation in any other interventional trial within 4 weeks prior to screening. 18. Inability to fully comprehend and/or perform study procedures or provide written consent in the Investigator's opinion. 19. Subject is not using adequate contraceptive precautions during the study and for up to 1 month after the last dose of the study medication. A highly effective method of birth control is defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intra-uterine devices, sexual abstinence or vasectomised partner. 20. Subject previously has entered this study. 21. Subject will not be available for follow-up assessments.
Primary and Secondary Endpoints:	<u>Primary Endpoint</u>: • The proportion of responders defined as subjects who have a decrease in total score of PFS (mean of items 2 to 23) of at least 1 point from baseline on Day 56.

Primary and Secondary Endpoints: (Cont'd)	Secondary Endpoints: • Proportion of subjects with a decrease of at least 60 msec from baseline on cognitive function tests (CFT) (total score) compared with placebo on Day 56. • Mean change from baseline in CFT total score compared with placebo. • Mean change from baseline in cognitive function subtasks scores compared with placebo. • Proportion of subjects who discontinue early due to lack of efficacy (no improvement, exacerbation of symptoms or worsening of fatigue). • Mean change from baseline in PFS total score (mean of item 2 to 23) compared with placebo. • Mean change from baseline in PFS of each of the 4 domains subscale scores compared with placebo on Day 56. • Mean change from baseline in SF-12 total score compared with placebo on Day 56 (or early termination). • Mean change from baseline in the mental health summary measures of SF-12 on Day 56 (or early termination). • Mean change from baseline in physical health summary scores of SF-12 on Day 56 (or early termination). • Mean change from baseline in restless leg syndrome rating scale score compared with placebo if applicable. • Proportion of subjects with Hb ≥120 g/L; s-ferritin ≥50 mcg/L; TSAT >20%. • Relationships between change in s-ferritin level and improvement on PFS on Day 56. • Relationships between change in s-ferritin level and success rate (decrease of at least 60 msec) of CFT on Day 56. Safety Endpoints: • Frequency of adverse events (AE). • Frequency of abnormal laboratory parameters. • Haematology: (complete blood count, s-ferritin, TSAT, soluble transferrin receptor, serum iron) • Blood biochemistry: alanine aminotransferase, aspartate aminotransferase and phosphate

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Procedures:	See Table 3 for full details of protocol required procedures and applicable visits (and timings). Visits were conducted at screening (V1), baseline (V2) where study drug was administered and thereafter at Day 7 (V3), 28 (V4) and 56 (V5). The PFS questionnaire was assessed at all visits whilst haematological parameters were assessed at Visits 1, 3, 4 and 5 and at Visits 1, 3 and 5 for biochemistry. Adverse events were collected at all visits.
Sample Size:	Planned: 288 subjects to be randomised (1:1 randomisation) to receive treatment with either FCM or placebo. Actual: The total number of randomised and treated subjects was 294 (145 in the FCM group and 149 in the placebo group). A 2-group χ^2-test with a 0.050 2-sided significance level and 80% power was chosen to detect the difference between the placebo group proportion ($P_{placebo}$ of 0.500) and the FCM group proportion (P_{FCM} of 0.670) resulting in a sample size of 131 in each group. A drop-out rate of approximately 10% was assumed, which resulted in a total of 288 subjects required for this study (144 per treatment arm). Drop-out patients were not replaced.
Statistical Methods:	<u>Randomisation</u> Block randomisation schemes were applied, whereby blocks refer to centres. <u>Statistical Methods for Analysis</u> Descriptive statistics: contingency tables (categorically scaled variables by treatment: absolute and relative frequencies) and tables (mean, standard deviation, SE, median, interquartile range, minimum, maximum; by treatment) for continuously scaled variables. <u>Primary Objective</u> Comparison of fractions P_{FCM} and $P_{placebo}$ of subjects with improvement of total sum (PFS) ≥ 1 via χ^2–test (2-sided, alpha-level: 0.05). Null hypothesis: $P_{FCM}=P_{placebo}$. <u>Secondary and Further Objectives</u> Differences between groups: Statistical tests were performed, results were reported in a descriptive manner fractions: χ^2-test, means/medians: t-test or Mann-Whitney U-test depending on distribution. Relationships between parameters: Correlation analysis (Pearson, Rank-Spearman) depending on distribution. <u>Further Evaluations</u> Evaluation of centre effects, influence of baseline values, analysis of interactions: general linear (mixed) models. <u>Analysis Population</u> Primary: intent-to-treat, secondary: per-protocol.

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Summary of Efficacy:	Of the 294 subjects randomised and starting treatment, 145 subjects were assigned to the iron-repletion group (and received FCM) and 149 were assigned to the control arm (and received placebo). The primary endpoint was defined as the proportion of patients with improvement of symptoms defined by a decrease of total PFS score (mean of items 2 to 23) of at least 1 point from baseline (V2) compared to Day 56 (V5). The total PFS score improved in 65.3% of the patients in the FCM group and in 52.7% in the placebo group. Based on the χ^2-test there was a statistically significant difference in favour of FCM when compared to placebo (95% CI 1.05-2.70; p=0.03). Therefore, it can be concluded that FCM is effective in improving fatigue symptoms as measured by the PFS in women of child bearing age with IDNA. The results of the SF-12 quality of life (QoL) questionnaire showed statistically significant differences for the "Mental Health" scores for the patients treated with FCM at Day 56 when compared to placebo. These results demonstrated that patients receiving FCM had a significant improvement in QoL as measured by the SF-12 questionnaire. In addition to the CFTs, 3 subtotals ("self-rated alertness", "self-rated contentment" and "self-rated calmness") were derived from 16 individual Bond-Lader computerised visual analogue scales related to mood and alertness. In the FCM group, treatment-related statistical significance in change from baseline to Day 56 (V5) was found for the subtotals "self-rated alertness" (p=0.007) and "self-rated contentment" (p=0.023) while this was not significant but showed a trend for the subtotal "self-rated calmness" (p=0.077). These findings further emphasised the improvement in overall QoL in women with iron deficiency and symptomatic fatigue after a single application of 1,000 mg iron as FCM. A statistically significantly higher proportion of patients reached normal Hb values (100%; normal defined as Hb ≥120 g/L), TSAT values (81.3%; normal defined as TSAT ≥20%) and s-ferritin (99.3%; normal defined as s-ferritin >50 mcg/L) in the FCM group when compared with the placebo group (p<0.0001). Statistically significant improvement was also found for all 3 conditions combined (81.3%) at Day 56 (V5; p<0.0001) when comparing treatment groups. The sensitivity analyses performed using different derivations of the primary endpoint, adjusting for baseline prognostic factors and based on different study populations, supported the outcome of the primary endpoint as described above.

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Summary of Safety:	The safety population included 145 subjects exposed to FCM and 149 subjects to placebo. All subjects received the full dose of 1,000 mg iron as FCM or the equivalent dosing of placebo, leading to 100% compliance. On average the subjects received doses of 16 mg/kg BW of iron as FCM; range from 11 mg/kg (90 kg BW) to 20 mg/kg (50 kg BW).A high number of enrolled subjects completed the trial: 283 subjects (96.3%) in total, 142 subjects (97.9%) in the FCM group and 141 (94.6%) in the placebo group. A total of 11 patients withdrew prematurely, 3 (2.1%) in the FCM group and 8 (5.4%) in the placebo group. The percentage of patients experiencing any treatment-emergent adverse event (TEAE) was higher in the FCM group (57.2%, 209 events, 83 patients) compared to the placebo group (49.0%, 114 events, 73 patients). In the FCM group, the most commonly (≥5% of subjects) experienced TEAEs by preferred term were headache (15.9%), nasopharyngitis (9.0%), pyrexia (8.3%) and nausea (5.5%) whilst these were headache (10.7%) and nasopharyngitis (5.4%) in the placebo group. The proportion of TEAEs that were rated mild or moderate within each treatment group was comparable (FCM 66.5% and 28.2%, placebo 63.2% and 36.8% respectively), while more patients in the FCM group experienced severe TEAEs compared to the placebo group (3.4% versus 0.0%). Within this study, reported causality information from individual events was converted from the World Health Organization causality scale to a binary scale (i.e., only into categories “related” and “unrelated”). The use of this binary causality scale may have therefore resulted in a higher number of cases being classified as related by the Investigator. Furthermore, the trial was single-blinded and over-reporting of severe AEs in the active drug group may be the result of a bias. No case of death was reported during the conduct of the study. There was 1 serious AE in the study which occurred in the FCM group, which was considered unrelated to FCM by the Investigator. No subjects in either group experienced an AE that led to premature discontinuation of study drug. Evaluations of vital signs and physical examinations showed no clinically important differences between subjects treated with FCM or placebo. For the iron related laboratory parameters, no negative clinical consequences, sequelae or interventions were associated with these changes. The achieved changes in the haematology values and iron parameters allowed patients values to return to desired normal ranges.

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Summary of Safety: (Cont'd)	Decreases in serum phosphate values were observed. The decreases in phosphate reached lowest values at V4 (28 Days), resolved spontaneously without intervention, and were not accompanied by clinical symptoms. No other clinically meaningful differences between the treatment groups were observed in the analyses of clinical chemistry or urinalysis variables. There were no relevant changes from baseline with regard to abnormal physical examination findings during the study in any body system in any treatment group. The overall safety evaluation indicates a positive benefit/risk ratio for the treatment of iron-deficient patients with 1,000 mg of iron administered as FCM. No new risks or AEs were identified from this study. The related AEs were consistent with the approved summary of product characteristics for the study drug.
Conclusion:	A single IV administration of 1,000 mg iron as FCM significantly and rapidly reduced symptomatic fatigue in IDNA women of child bearing age. There were no new safety findings in this study, and FCM treatment was well tolerated. The results of this placebo-controlled study confirm that iron deficiency without anaemia can affect women's QoL, and emphasise the importance of maintaining a normal iron status independent of Hb levels.