## CLINICAL STUDY SYNOPSIS

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| **Name of Company:**<br>**Vifor Pharma – Vifor (International) AG** |
| **Name of Finished Product:**<br>**FERINJECT®** |
| **Name of Active Ingredient(s):**<br>**Ferric carboxymaltose** |

**Title of Study:** A multi-centre, randomized, prospective, single-blinded, controlled study to investigate the efficacy and safety of a standardized maintenance dosage regimen of intravenous ferric carboxymaltose (FERINJECT®) versus PLACEBO in patients with iron deficiency caused by inflammatory bowel disease

**Protocol Number:** FER-IBD-07-MAIN

**Study Period:** **Phase of Development:** IIIb

**Date of first enrolment:** 14 Feb 2009

**Date of last completed:** 13 Oct 2010

**Investigators and Study Centres:**

The study was performed in 69 active centres in Russia (21 centres), Ukraine (11), Germany (11), Sweden (4), United Kingdom (4), Romania (4), Austria (3), Denmark (3), Estonia (2), Norway (2), Switzerland (2), France (1) and Spain (1).

**Publication(s):** Not applicable.

**Objectives:**

Primary objective:

- To evaluate the efficacy and safety of a standardised maintenance dosage regimen of FERINJECT® versus PLACEBO in the correction of iron deficiency and prevention of anaemia over 8 months.

Secondary objectives:

- To evaluate the efficacy of treatment with FERINJECT® in respect to health related Quality of Life (QoL) over 8 months.
- To evaluate the safety and tolerability of a standardised maintenance dosage regimen of FERINJECT®.
- To evaluate the effect of treatment with FERINJECT® over 8 months on the development of underlying disease.

**Study Design:** Multi-centre, randomised, prospective, single-blinded, controlled study.

**Number of Patients (planned and analysed):**

Planned: 200 patients to be randomised to receive treatment with either FERINJECT® or PLACEBO.

Actual: A total of 262 patients were screened of which 245 were randomised and had at least 1 post-baseline visit (105 in the FERINJECT® group, 99 in the PLACEBO group and 41 who were randomised but did not receive treatment).

| Safety Set | FERINJECT® (N = 105) | PLACEBO (N = 99) | No Treatment (N = 41) | Total (N = 245) |
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Patients who did not require treatment at any time during the study (22 in the FERINJECT® group and 19 in the PLACEBO group) were excluded from the Full Analysis Set (FAS). Patients who had major protocol violations were also excluded from the Per-Protocol Set (PPS).

A modified FAS (mFAS) analysed patients by the group they were randomised to and included patients that did not have any treatment.

The analysis populations were as follows:

| **Analysis populations** | **FERINJECT® (N = 133) n (%)** | **PLACEBO (N = 123) n (%)** | **Total (N = 256) n (%)** |
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| Full Analysis Set | 105 (78.9) | 99 (80.5) | 204 (79.7) |
| Per-Protocol Set | 85 (63.9) | 85 (69.1) | 170 (66.4) |
| Modified FAS | 127 (95.5) | 118 (95.9) | 245 (95.7) |

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**Diagnosis and Main Criteria for Inclusion:**

Male and female patients ≥18 years of age who participated in the FER-IBD-07-COR study and were non-anaemic at the End of Study Visit (Hb ≥12 g/dL female, ≥13 g/dL male), independent of serum ferritin value.

**Test Product, Dose and Mode of Administration, and Lot Number(s):**

FERINJECT® 500 mg (diluted in 0.9% sodium chloride solution for intravenous infusion) administered up to 5 times (at baseline and after 2, 4, 6 and 8 months) via intravenous drip infusion, if patient's serum ferritin level measured at the respective visit was <100 µg/L.
Per Vifor (International) Inc. CofC 02-Dec-2008, Ferinject Lot No.: 808007-117889.

**Reference Therapy, Dose and Mode of Administration, and Lot Number(s):**

PLACEBO (250 mL 0.9% sodium chloride solution) administered up to 5 times (on baseline and after 2, 4, 6 and 8 months) via intravenous drip infusion, if patient's serum ferritin level measured at the visit was <100 µg/L.
Placebo 0.9% sodium chloride solution for infusion from the hospital's stock was used.

**Duration of Treatment:** Up to 8 months

**Criteria for Evaluation:**

*Efficacy:*

Haemoglobin (Hb), health-related Quality of Life (QoL) measured with the SF-36 version 2 and the Intestinal Bowel Disease Questionnaire (IBDQ), change in disease activity assessment (using modified Crohn's Disease Activity Index [CDAI], modified Colitis Activity Index [CAI], and C-reactive protein (CRP), and days out of work due to IBD or anaemia.

*Safety:*

Adverse events (AEs), vital signs, physical examination, laboratory tests (haematology, clinical chemistry, urinalysis, iron status), and days of hospitalisation due to IBD or anaemia.

**Statistical Methods:**

*Determination of Sample Size:*

The sample size was a consequence of the preceding FER-IBD-07-COR study, assuming that approximately 50% of patients from this study will enrol into FER-IBD-07-MAIN. As a conservative estimate it was assumed that 80 patients per treatment group would have evaluable data for the primary analysis; therefore a 5% level two-sided log-rank test for equality of time-to-event curves would have 80% power ($\beta$=0.10) to detect the difference at t=8 months between a Group 1 proportion of 20% and a Group 2 proportion of 40% of patients becoming anaemic (assuming a constant hazard ratio of 0.5).

*Efficacy Evaluation:*

The time to development of anaemia was summarised by treatment group using Kaplan-Meier survival curves. Estimated probabilities of development of anaemia at 60-day intervals were presented for each treatment group along with 95% CIs. Treatment groups were compared using a log-rank test. An estimate of the treatment Hazard Ratio (HR) based on the log-rank test was provided together with a corresponding 95% CI.

All secondary efficacy endpoints were summarised descriptively and changes from baseline displayed. Additionally comparisons between treatment groups were performed using analysis of covariance (ANCOVA) for SF-36 and IBDQ, and logistic regression for number of patients with haemoglobin <12 g/dL (female) or <13 g/dL (male).

*Safety Evaluation:*

All safety analyses were based upon the Safety Set. All safety variables were presented in by-patient listings, sorted by treatment group, geographic region, centre and patient identifier. Patients who did not receive treatment were summarised in a "No Treatment" group. The baseline value of each safety laboratory test, vital sign or physical examination endpoint was defined as the value recorded at the screening visit. Data were summarised in frequency tables or using descriptive statistics as applicable. Shift tables were also produced for laboratory evaluations. In addition, the changes from baseline to months 2, 4, 6 and 8 in haemoglobin, serum ferritin and transferrin saturation (TfS) were analyzed (for the full analysis set) using ANCOVA for each month.

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**Efficacy Results:**

The primary objective of the study was to evaluate the efficacy and safety of a standardised maintenance dosage regimen of FERINJECT® versus PLACEBO in the correction of iron deficiency and prevention of anaemia in treatment over 8 months.

In the FAS population, 28 out of 105 (26.7%) patients became anaemic in the FERINJECT® group compared with 39 of 99 (39.4%) in the PLACEBO group during the 8 month study period. The time to 25% of patients developing anaemia was 7.62 months in the FERINJECT® group compared with 4.67 months in the PLACEBO group. For the primary endpoint, the probability of developing anaemia (based on Greenwood's formula for the standard error of the Kaplan-Meier estimate) was calculated to be 10.5%, 16.2%, 21.0%, and 27.2% in the FERINJECT® group and 15.2%, 23.3%, 32.8%, and 40.4% in the PLACEBO group at Months 2, 4, 6, and 8 respectively. Based on the log-rank test there was a statistically significant difference in favour of FERINJECT® compared to PLACEBO (p=0.049). The hazard ratio was 0.62 (95% CI: 0.38 to 1.00) indicating a lower risk of developing anaemia with FERINJECT® than with PLACEBO.

The sensitivity analyses performed using a different derivation of the primary endpoint (midpoint rather than linear interpolation), adjusting for baseline prognostic factors and based on different study populations (PPS and modified FAS) supported these results, although these were not statistically significant.

Results of the ANCOVA of the SF-36 scores showed no statistically significant differences in the mean change from baseline to Months 2 and 8 between the FERINJECT® group and the PLACEBO group in all 8 dimensions of health (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health) and in both the physical and mental components summaries.

Results of the ANCOVA of the IBDQ scores showed no statistically significant differences in the mean change from baseline to Month 2 and 8 between the FERINJECT® group and the PLACEBO group for the dimensions bowel symptoms, systemic symptoms, emotional status, social functioning, and for the total score.

A smaller proportion of patients became anaemic in the FERINJECT® group than in the PLACEBO group at each study visit. At Months 2, 4, 6, and 8, respectively, 10.5%, 9.4%, 7.9%, and 10.8% of patients in the FERINJECT® group, and 14.1%, 11.9%, 13.5%, and 16.7% in the PLACEBO group became anaemic. The differences between the groups were not statistically significant.

There was no change in the modified CDAI and CAI score, neither for the subscores nor for the total score, in any treatment group. Mean CRP values were stable in both treatment groups.

Overall, 18 (8.8%) patients had at least one day out of work during the study due to IBD, 7 (6.7%) in the FERINJECT® group and 11 (11.1%) in the PLACEBO group. No patient was out of work due to anaemia. The mean percentage of days out of work during the study was 21.79% in the FERINJECT® group and 9.59% in the PLACEBO group (this percentage describes number of days out of work in relation to the number of days in the study).

**Safety Results:**

The mean (SD) exposure of drug given during the study amounted to 1181.0 (661.9) mg FERINJECT® (corresponding to 590.5 [331.0] mL solution), and 753.4 (397.9) mL PLACEBO solution. At all visits after baseline, the proportion of patients requiring infusions was lower in the FERINJECT® group compared to the PLACEBO group.

The percentage of patients experiencing any TEAE was similar between the FERINJECT® group (59.0%) and the PLACEBO group (50.5%), and lower in patients receiving no treatment (39.0%).

More patients in the FERINJECT® group experienced severe TEAEs compared to the PLACEBO group (9.5% versus 4.0%) as well as TEAEs considered related to the study drug (7.6% versus 1.0%), and events leading to permanent discontinuation of the study drug (2.9% versus 0.0%). The percentage

of patients experiencing SAEs was comparable (6.7% versus 8.1%). No patients died during the study.

The most common TEAEs (by SOC) occurred in the SOC Gastrointestinal Disorders (21.6% of patients overall, 20.0% in the FERINJECT® group, 26.3% in the PLACEBO group, and no patients in the No Treatment group), Infections and Infestations (16.7%, 22.9%, 14.1%, and 7.3%, respectively), and Investigations (9.4%, 10.5%, 10.1%, and 4.9%, respectively).

The most common TEAEs (by PT) were ulcerative colitis (exacerbation of underlying disease) (7.8% of patients overall, 6.7% in the FERINJECT® group, and 12.1% in the PLACEBO group) and nasopharyngitis (7.3%, 9.5%, and 7.1%, respectively).

Overall, 68 (27.8%) patients had TEAEs of mild intensity and 46 (18.8%) patients had TEAEs of moderate intensity. Overall, 14 (5.7%) patients had TEAEs of severe intensity; 10 (9.5%) patients in the FERINJECT® group and 4 (4.0%) patients in the PLACEBO group. There were no severe TEAEs in the No Treatment group. The 10 severe events in the FERINJECT® group were ulcerative colitis (exacerbation of underlying disease), abdominal pain (2 patients), Crohn's disease (exacerbation of underlying disease), viral respiratory tract infection, infected dermatitis, back pain (2 patients), polyarthritis, and respiratory disorder. The 4 severe events in the PLACEBO group were ulcerative colitis (2 patients), increased aspartate aminotransferase, and headache.

Overall, 104 (42.4%) patients had TEAEs that were not related to the study drug. The relationship to the study drug was unlikely in 15 (6.1%) patients, possible in 6 (2.4%) patients, probable in 2 (0.8%) patients, and certain in 1 (0.4%) patient.

The majority of study drug-related TEAEs – defined as all TEAEs judged by the investigator to be possibly, probably or certainly related to the study drug, or for which a relation to the study drug was not assessed – were reported in the SOC Investigations (2.4% overall, 4.8% of patients in the FERINJECT® group and 1.0% of patients in the PLACEBO group). Most common study drug-related TEAE was increased alanine aminotransferase (overall 3 [1.2%] patients). All of the study drug-related TEAEs were of mild or moderate intensity; none were of severe intensity.

Overall, 18 (7.3%) patients experienced 26 SAEs. The incidence of SAEs was comparable between the groups in all SOCs. The majority of SAEs were in the SOC gastrointestinal disorders, which occurred in 15 (6.1%) patients overall (4.8% in the FERINJECT® group, 8.1% in the PLACEBO group, and 4.9% in the No Treatment group). Ulcerative colitis and Crohn's disease (exacerbation of the respective underlying disease) were the most commonly reported SAEs, reported by overall 8 (3.3%) and 4 (1.6%) patients, respectively. The SAEs of ulcerative colitis (3 patients), Crohn's disease, colonic fistula, infected dermatitis, polyarthritis, and pulmonary embolism were of severe intensity. All of the SAEs were considered unrelated to the study drug.

Overall, 3 (1.2%) patients had TEAEs leading to permanent discontinuation of the study drug. The TEAEs leading to discontinuation were increased alanine aminotransferase, increased aspartate aminotransferase, and pancreatitis. All events occurred in the FERINJECT® group. All events were of moderate intensity. The event of pancreatitis was considered as not related to the study drug. The events of increased alanine aminotransferase and increased aspartate aminotransferase were considered as possibly related to the study drug.

There was 1 patient with an anaphylactic reaction (FERINJECT® group), which was considered as moderate. The anaphylactic reaction (dyspnea and chest tightness) occurred 6 months after the last dose of study drug and was considered related to infliximab infusion given 10 minutes before the onset of symptoms. There were no infusion site reactions reported in any patient.

An analysis of change from baseline in Hb showed statistically significant differences between the FERINJECT® and PLACEBO group with regard to changes at Months 4, 6, and 8 ($p=0.041$, $p=0.008$ and $p=0.018$). At these visits, the mean Hb value increased in the FERINJECT® group, whereas it only slightly increased or decreased in the PLACEBO group. The mean values for reticulocytes increased in both the FERINJECT® and PLACEBO group from baseline to Month 2, and remained increased until Month 8. No such increase was observed in the No Treatment group. Other changes in haematology and clinical chemistry parameters during the study were minimal and without any obvious pattern of

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change.

There were only minimal changes of urine phosphate mean values during the study in any group without a clear pattern.

With regard to the iron status, in the FERINJECT® group, the adjusted mean serum ferritin level increased from baseline to Month 8 with 30.34 µg/L, whereas in the PLACEBO group, it decreased from baseline to Month 8 with 36.14 µg/L. An analysis of change from baseline in serum ferritin showed statistically significant differences between the FERINJECT® and PLACEBO group at all visits ($p<0.001$). Regarding transferrin, in all treatment groups, the mean changes from baseline over time were minimal and without any obvious pattern of change. The adjusted mean TfS level increased from baseline of 21.77% to Month 8 by 0.58% in the FERINJECT® group, whereas it decreased by 4.00% in the PLACEBO group. An analysis of change from baseline in TfS showed statistically significant differences between the FERINJECT® and PLACEBO group at Months 4, 6, and 8 ($p=0.014$, $p=0.002$, and $p=0.022$, respectively).

Overall, 15 (6.1%) patients had at least one day in hospital during the study due to IBD, 6 (5.7%) in the FERINJECT® group, 7 (7.1%) in the PLACEBO group, and 2 (4.9%) in the No Treatment group. No patients were hospitalised due to anaemia. The mean percentage of days in hospital during the study was 8.12% in the FERINJECT® group, 8.76% in the PLACEBO group, and 9.23% in the No Treatment group (this percentage describes the number of days in hospital in relation to the number of days in the study).

Mean values for vital signs (systolic and diastolic blood pressures, heart rate and body temperature) showed only minimal changes from baseline and were similar between the treatment groups. 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.

**Conclusions:**

- In non-anaemic IBD patients recently treated with IV iron (to correct anaemia), bi-monthly serum ferritin triggered maintenance infusions of 500 mg iron as FERINJECT® effectively reduced the proportion of patients becoming anaemic as compared to PLACEBO: estimated percentages of patients likely to develop anaemia within 8 months of randomisation; 27.2% for FERINJECT® vs. 40.4% for PLACEBO; hazard ratio=0.62 (95% CI 0.38-1.00; p=0.049).
- There was no statistically significant difference in the secondary endpoints regarding changes in quality of life (IBDQ and SF-36) and changes in disease activity between patients treated with FERINJECT® compared to PLACEBO.
- There were comparable proportions of patients experiencing an AE or SAE in all treatment groups. There were no new safety findings in this study, and FERINJECT® treatment was well tolerated. No patient died during this study.
- The results from this study are in line with previous findings in studies with FERINJECT®, and therefore, there is no change to the benefit-risk-profile of FERINJECT®.