# CLINICAL STUDY SYNOPSIS

**Name of Company:** Vifor Pharma – Vifor (International) AG
**Volume:** (For national authority use only)
**Name of Finished Product:** FERINJECT®
**Page:**
**Name of Active Ingredient:** Ferric carboxymaltose

**Title of Study:** A multi-centre, randomised, prospective, open-label study to investigate the efficacy and safety of a standardised correction dosage regimen of intravenous ferric carboxymaltose (FERINJECT®) versus iron sucrose (VENOFER®) for treatment of iron deficiency anaemia in patients with inflammatory bowel disease

**Protocol Number:** 93842

**Study Period:**
**Phase of Development:** IIIb
**Date of first enrolment:** 24 Oct 2008
**Date of last completed:** 10 Dec 2009

**Investigators and Study Centres:**
The study was performed in 88 active centres in Austria, Denmark, Estonia, France, Germany, Lithuania, Norway, Romania, Russia, Spain, Sweden, Switzerland, Ukraine and the United Kingdom.

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

**Objectives:**
Primary objective:
- To evaluate the non-inferiority in efficacy of a standardised dosage regimen of FERINJECT® compared to individually calculated dosage regimens of VENOFER® in the correction of iron deficiency anaemia (IDA) in patients with inflammatory bowel disease (IBD) in remission.

Secondary objective:
- To evaluate the safety and tolerability of a standardised correction dose regimen of FERINJECT®.

**Study Design:** Multi-centre, randomised, prospective, open-label, controlled study.

**Number of Subjects (planned and analysed):**
Planned: 420 subjects to be randomised (1:1 randomisation) to receive treatment with either a standardised correction dosage regimen of FERINJECT® or individually calculated dosage regimens of VENOFER®.
Actual: The total number randomised subjects was 485, the total number of randomised and treated subjects was 483.

| Analysis populations | FERINJECT® (N = 244) n (%) | VENOFER® (N = 241) n (%) | Total (N = 485) n (%) |
|---|---|---|---|
| Safety set | 244 (100.0) | 239 (99.2) | 483 (99.6) |
| Full analysis set | 240 (98.4) | 235 (97.5) | 475 (97.9) |
| Per-protocol set | 227 (93.0) | 189 (78.4) | 416 (85.8) |

**Diagnosis and Main Criteria for Inclusion:**
Male and female subjects ≥18 years of age suffering from mild IBD (Crohn's disease or ulcerative colitis) or in remission with ferritin <100 µg/L.

**Test Product, Dose and Mode of Administration, and Lot Number(s):**
FERINJECT® to be administered up to 3 times (on Days 1, 8 and 15) according to the subject's haemoglobin level and body weight via intravenous drip infusion.
Per Catalent CofC 09Jan2009 and 06Feb2009, Ferinject Lot No.: 834000.

**Reference Therapy, Dose and Mode of Administration, and Lot Number(s):**
VENOFER® to be administered up to 11 infusions twice a week (on Days 1, 4, 8, 11, 15, 18, 22, 25, 29, 32 and 35) based on the subjects individually calculated iron deficit via intravenous drip infusion.
Per Catalent CofC 09Jan2009 and 06Feb2009, Venofer Lot No.: 849200.

**Duration of Treatment:** Up to 35 days.

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**Criteria for Evaluation:**

*Efficacy:*

Haemoglobin (Hb), serum ferritin, transferrin, transferrin saturation (TfS), health-related Quality of Life (QoL) using the SF-36 version 2, and Intestinal Bowel Disease Questionnaire (IBDQ).

*Safety:*

Laboratory parameters: ferritin, transferrin, TfS, Hb, haematocrit (Hct), red blood cell (RBC) count, erythrocyte sedimentation rate (ESR), white blood cell (WBC) count with differential and platelet count, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), reticulocytes, alanine aminotransferase (ALT), aspartate aminotransferase (AST), sodium, potassium, albumin, lactate dehydrogenase (LDH), C-reactive protein (CRP), creatinine, phosphate, vitamin $B_{12}$, folic acid and urinalysis with phosphate in spontaneous urine. Vital signs, electrocardiogram (ECG), change in disease activity assessment (using Crohn's Disease Activity Index [CDAI], Colitis Activity Index [CAI] and CRP), days out of work or hospitalised due to IBD, and adverse events (AEs).

**Statistical Methods:**

*Determination of Sample Size:*

Sample sizes of 183 in both the FERINJECT® standardised correction dosage group and the VENOFER® group provided basis for achieving 90% power ($\beta$=0.10) at a 2.5% significance level by using a one-sided equivalence test of proportions when the proportion for the FERINJECT® group with standardised correction dosage regiment was 0.82 and the proportion in the VENOFER® group being tested for equivalence was 0.75, and the maximum allowable difference between these proportions that would conclude that they were equivalent (the range of equivalence) was 0.07. Assuming a dropout rate of 15%, a total of 420 subjects needed to be randomized for ensuring 366 subjects completing the study.

*Analysis Populations:*

The following 3 definitions of analysis populations were used for the data analysis and tabulations.

Safety Set: All randomized subjects who received at least 1 dose of study treatment. Subjects were included in the analysis according to the treatment received.

Full Analysis Set (FAS): All randomised subjects who received at least 1 dose of study drug and who attended at least one post baseline visit, following the principle of intention-to-treat (ITT). Subjects were included in the analysis according to the treatment to which they were randomized.

Per-Protocol Set (PPS): All randomised subjects who were compliant with the study protocol, i.e., who did not experience any major protocol deviations.

*Efficacy Evaluation:*

All efficacy analyses were presented for the FAS and for the PPS. The primary endpoint was the number of responders as defined by an increase in Hb of at least 2 g/dl at week 12 as compared to baseline. Hb increase is derived as the change in Hb measurement at Week 12 from baseline and responder status is defined as follows: Hb increase ≥2 g/dL: response. Evaluation was done by a one-sided 97.5% confidence interval evaluated by a non-inferiority margin of 7%.

*Safety Evaluation:*

Medical and surgical history was coded with the Medical Dictionary for Regulatory Activities (MedDRA), version 11.1. Findings were summarised by system organ class (SOC) and preferred term (PT). Prior medication, prior and concomitant medication, and concomitant medication were presented by World Health Organisation - Anatomical Therapeutic Chemical - Drug Reference List (WHO-ATC-DRL) classification level 1 (main groups), level 2 (pharmacological/therapeutic subgroups) and PT. Summaries and analyses of AEs were based on TEAEs, which were defined as AEs occurring on or after the day of the first administration of study treatment or AEs present before first administration of study treatment and ongoing after administration with increased severity. Other AEs (pre-treatment AEs) were only listed.

**Efficacy Results:**

The primary objective of the study was to demonstrate non-inferiority in efficacy of a standardised dosage

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regimen of FERINJECT® compared to individually calculated dosage regimens of VENOFER® in the correction of IDA in subjects with IBD in remission. In the PPS, the percentage of responders (Hb increase ≥2 g/dL at Week 12) was 66.06% in the FERINJECT® group and 54.14% in the VENOFER® group. The percentage was 11.91% (95% CI: 2.28, 21.31) higher in the FERINJECT® group than the VENOFER® group. In the FAS (observed case), the percentage of responders was 65.79% in the FERINJECT® group and 53.64% in the VENOFER® group. The percentage was 12.15% (3.07, 20.97) higher in the FERINJECT® group than the VENOFER® group. Since the lower limit of the CIs in both analysis sets were greater than -7%, FERINJECT® has demonstrated to be non-inferior to VENOFER® in efficacy in subjects with IBD in remission. The results of the primary endpoint were robust as confirmed in additional methods/populations (FAS last observation carried forward [LOCF] and FAS worst case). Since p-values showed statistical significance in all analysis sets, superiority of FERINJECT® compared to VENOFER® could be declared.

Results of the secondary endpoints analyses consistently showed that the percentages of responders in the FERINJECT® group were higher than those in the VENOFER® group. Results of the repeated measures analyses of the change from baseline in Hb levels, ferritin levels and TfS scores showed that the FERINJECT® group had a higher change from baseline than the VENOFER® group at all time points and the FERINJECT® group had a statistically significantly higher increase in Hb levels (except Week 1), ferritin levels and TfS scores than the VENOFER® group at all time points regardless of gender, baseline haemoglobin and baseline disease status.

In terms of health-related QoL evaluation based on QoL questionnaire SF 36 version 2 and IBDQ, the results showed that the mean change of scores from baseline to Week 12 was higher in the FERINJECT® group than the VENOFER® group in most health dimensions although no statistically significant differences between the two treatment groups were observed.

Subgroup analyses showed that the subjects who had an Hb level of ≥7 and <10 g/dL at baseline, had higher responder rates than subjects who had an Hb level of ≥10 and ≤12 g/dL (for females) ≤13 g/dL (for males) at baseline. This was true for both treatment groups.

**Safety Results:**

The mean (SD) of the total number of infusions in the FERINJECT® group was 2.1 (0.6), which was lower than in the VENOFER® group (5.8 [1.6]). This was because the subjects in the FERINJECT® group were to receive up to 3 infusions, whereas the subjects in the VENOFER® group received the number of infusions based on individual iron deficit. The mean (SD) of the true total dose of iron was 1413.6 (325.8) mg and 1206.7 (253.2) mg in the FERINJECT® and VENOFER® group, respectively.

The percentage of subjects experiencing TEAEs (overall, severe TEAEs, serious TEAEs, study drug-related TEAEs, and TEAEs leading to permanent discontinuation) was similar between the FERINJECT® group and the VENOFER® group. Overall, there were 234 (48.4%) subjects experiencing any TEAE, 10 (2.1%) subjects had a severe TEAE, 22 (4.6%) subjects had a serious TEAE, and 11 (2.3%) subjects had a TEAE leading to discontinuation of the study drug. No subjects died in this study. The most common TEAEs (by PT) were nasopharyngitis in overall 21 (4.3%) subjects and ulcerative colitis in 20 (4.1%) subjects.

The percentage of subjects experiencing study drug-related TEAEs was similar between the FERINJECT® group (34 [13.9%) subjects) and the VENOFER® group (27 [11.3%) subjects). One (0.4%) subject in the FERINJECT® group and no subject in the VENOFER® group experienced any study drug-related severe or serious event. The most common study drug-related TEAEs were serum ferritin increased (overall 1.7%) and blood phosphorus decreased (overall 1.2%), which more frequently occurred in the FERINJECT® group (2.9% and 2.5%) compared to the VENOFER® group (0.4% and 0%).

Overall, 6 subjects (2.5%) in the VENOFER® group and 1 subject (0.4%) in the FERINJECT® group experienced infusion site TEAEs. All the infusion site TEAEs were of mild or moderate intensity and were considered related to the study drugs by the investigator.

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With regard to safety laboratory parameters, for phosphate, there was a trend for a decrease in mean values from baseline to Week 4 and an increasing trend from Week 8 to Week 12 in the FERINJECT® group, but the mean changes remained fairly constant over time in the VENOFER® group. There were minimal mean changes from baseline at all visits over time for sodium, potassium, creatinine and LDH in both treatment groups. For albumin, there was an increase from baseline at all visits in both treatment groups except at Week 8 and Week 12 in the FERINJECT® group and Week 12 in the VENOFER® group. For ALT and AST, there was an increasing trend in mean values from baseline to Week 4 and a decreasing trend from Week 8 to Week 12 in both treatment groups. The mean values of CRP decreased from screening to baseline in both treatment groups and then fluctuated without a clear trend in both treatment groups from baseline to Week 12. There were only small mean changes (increase and decrease) in urine phosphate at all visits.
There were no relevant changes in vital signs or ECG findings in both treatment groups.

**Conclusions:**

- The non-inferiority of FERINJECT® versus VENOFER® was demonstrated as the lower limit of the CIs of the difference in percentage of responders in both the FAS and the PPS (12.15% and 11.91%, respectively, higher in the FERINJECT® group) were greater than -7%. The results were robust in 2 additional methods/populations (FAS LOCF and FAS worst case). Since p-values showed statistical significance in all analysis sets, superiority of FERINJECT® compared to VENOFER® could be declared.
- FERINJECT® showed an improved Hb change efficacy (faster response and greater magnitude). Simpler dosing according to a standardised dosing regimen offers better compliance, better convenience and better efficacy.
- Results of the secondary endpoints analyses consistently showed that FERINJECT® performed significantly better than the VENOFER® group.
- No statistically significant differences were shown between the treatment groups with regards to QoL.
- The overall safety profile of FERINJECT® was as expected from previous studies. Based on the safety results in this study including the incidence of TEAEs, laboratory findings and changes in Crohn's disease and colitis activities, FERINJECT® was shown to be as safe and well tolerated as VENOFER®.
- The results of this study demonstrate that FERINJECT® is safe and well tolerated with an acceptable safety profile; and superior to VENOFER® in correcting IDA in subjects with mild IBD or IBD in remission.