SYNOPSIS

FER-FID-CHEMO

Name of Company:	Vifor (International) AG
Name of Finished Product:	Ferinject®
Name of Active Ingredient:	Ferric carboxymaltose (FCM)

Title:	A randomised, controlled, parallel-group, open-label study to evaluate the efficacy and safety of intravenous ferric carboxymaltose versus no treatment in anaemic subjects with lymphoid malignancies and functional iron deficiency receiving chemotherapy.
Short Title:	Ferric carboxymaltose (FCM) in the treatment of anaemia in subjects with lymphoid malignancies and functional iron deficiency (FID) who were receiving chemotherapy.
Indication:	Anaemic subjects with lymphoid malignancies and FID receiving chemotherapy.
Phase:	2
Study Code:	FER-FID-CHEMO
Co-ordinating Investigator:	Torbjörn Karlsson, MD, PhD (Uppsala, Sweden)
Study Centres:	A total of 30 sites participated in the study: 11 sites in Germany, 11 in Russia, 6 in Sweden, and 2 in Austria.
Objectives:	Primary Objective: • To evaluate the efficacy of FCM given without erythropoiesis stimulating agents (ESAs) in the correction of haemoglobin (Hb) levels in anaemic subjects with lymphoid malignancies who were undergoing chemotherapy. Secondary Objectives: • To evaluate the safety and tolerability of FCM. • To evaluate the effect of treatment with FCM on iron status variables in subjects suffering from lymphoid malignancies.
Design:	This was a Phase 2, multicentre, randomised, controlled, 2-arm, open-label, prospective pilot study to evaluate efficacy and safety of FCM in the treatment of anaemia in subjects with lymphoid malignancies who were receiving chemotherapy. After screening, which was performed within 28 days prior to the first infusion, eligible subjects were randomised (1:1) to Arm A to receive either 1,000 mg iron (as FCM as a single intravenous infusion or 2 infusions, each 500 mg iron as FCM) or to Arm B (no FCM infusion) to receive standard of care (the subjects were allowed to be treated according to the local institutional practice if required for symptomatic management of anaemia). Randomisation and baseline assessments were done on Day 1 prior to the first infusion of study drug.

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Design: (Cont'd)	All subjects were to return for assessments of safety and efficacy at Weeks 2, 4, 6, and 8. Forty subjects were planned to be included in this study. However, due to low recruitment, the Sponsor decided to stop recruitment after 19 subjects were randomised. As a result, this Clinical Study Report discusses the results of 19 randomised subjects.
Treatment:	Arm A: After randomisation, subjects were to receive a total dose of 1,000 mg iron as FCM on the first day of the next scheduled chemotherapy cycle or within 24 hours before or after receiving chemotherapy. In subjects weighing ≥50 kg, a single infusion of 1,000 mg iron as FCM was to be administered on Day 1 (Week 0). In subjects with body weight <50 kg, 2 infusions of FCM (500 mg each) were to be administered: the first on the day of the scheduled chemotherapy cycle (Day 1, Week 0) and the second at the next study visit (Week 2; Day 15 ± 3 days). If at Day 15 ± 3 days, the subject had an elevated transferrin saturation (TSAT) level (>50%) or elevated ferritin level (>800 ng/mL), or an elevation of liver enzymes over 3 times the upper limit of normal (ULN), or a blood transfusion since the first dose of FCM, then the second dose was to be withheld at Week 2; it was to be administered at the next study visit as long as the ferritin level was ≤800 ng/mL and TSAT <45%. Otherwise, the subject was to be discontinued from the study. In the case of subjects <50 kg who had a blood transfusion after the first infusion, the second transfusion was not to be administered at all. Arm B: No treatment. Subjects were to be treated according to the local institutional practice if management of symptomatic anaemia was required. Intravenous iron was to be used only to treat absolute iron deficiency (defined as ferritin less than the lower limit of normal based on the test reference ranges). Rescue medication to manage anaemia was permitted in both arms at the discretion of the treating physician and/or per institutional practice.
Inclusion Criteria:	1. Subjects (male or female) aged ≥18 years, suffering from indolent non-Hodgkin's lymphoma (NHL), multiple myeloma (MM), or chronic lymphocytic leukaemia (CLL) on any chemotherapy. 2. Life expectancy at least 6 months. 3. Received at least 8 weeks (or 2 cycles) of treatment in the current course of chemotherapy before start of iron therapy. 4. 8.5 g/dL ≤ Hb ≤10.5 g/dL at time of randomisation.

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Inclusion Criteria: (Cont'd)	5. Iron-restricted erythropoiesis defined as: • Stainable iron in bone marrow combined with TSAT ≤20%, OR • If the evaluation of stainable iron in bone marrow was not possible or available: – Ferritin >30 ng/mL (women) or >40 ng/mL (men) AND – TSAT ≤20% 6. Signed informed consent (before any study procedure). 7. Females of childbearing potential must have a negative urine pregnancy test.
Exclusion Criteria:	1. Any anaemia treatment within 4 weeks before inclusion (including red blood cell (RBC) transfusion, ESA treatment, and any oral/parenteral iron supplementation). 2. Subjects weighing <35 kg. 3. Subjects with increase in Hb during the chemotherapy (>1 g/dL rise between initiation of chemotherapy and screening laboratory value). 4. Folate deficiency (serum folate <4.5 nmol/L) and/or Vitamin B_{12} deficiency (serum cobalamin <145 pmol/L). 5. Ongoing haemolysis defined as serum-haptoglobin <0.2 g/L. 6. Recent significant bleeding/surgery. 7. Known chronic renal failure, creatinine >125 µmol/L. 8. Clinically relevant active inflammatory disease other than the malignant disease (according to the judgement of the Investigator). 9. Clinically relevant ongoing infectious disease including known human immunodeficiency virus. 10. Serum ferritin >800 ng/mL. 11. Ongoing significant neurological or psychiatric disorders including psychotic disorders or dementia. 12. Significant cardiovascular disease prior to study inclusion including myocardial infarction within 12 months prior to study inclusion, congestive heart failure of New York Heart Association Grade III or Grade IV, or poorly controlled hypertension according to the judgement of the Investigator. 13. Elevation of liver enzymes (aspartate aminotransferase, alanine aminotransferase) over 3 times the ULN range, or known acute hepatic disorder. 14. Subject was currently enrolled in or did not complete at least 30 days since ending other investigational device or drug study(ies), or subject was receiving other investigational agent(s).

Exclusion Criteria: (Cont'd)	15. Female subject was evidently pregnant (e.g., positive human chorionic gonadotropin test) or breastfeeding. 16. Female subject not using adequate contraceptive precautions. Adequate contraceptive precautions were 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. Non-childbearing potential included being surgically sterilised at least 6 months prior to the study or post-menopausal, defined as amenorrhea for at least 12 months. 17. Known sensitivity to any of the products to be administered during dosing. 18. Subject was not to be available for follow-up assessment. 19. Subject had any kind of disorder that compromised the ability of the subject to give written informed consent and/or to comply with study procedures.
Primary and Secondary Efficacy Endpoints and Safety Criteria:	Primary Efficacy Endpoint: • Mean change in Hb from baseline to Weeks 4, 6 and 8 (end of treatment) in the absence of any RBC transfusion or ESA treatment. Secondary Endpoints: • The percentage of subjects with blood Hb increase of at least 1 g/dL at any study week in the absence of any RBC transfusion or ESA treatment. • The percentage of subjects with an Hb correction to at least 11 g/dL in the absence of any RBC transfusion or ESA treatment. • The median time to Hb response defined as increase in Hb ≥1 g/dL in the absence of any RBC transfusion or ESA treatment. • The proportion of subjects receiving RBC transfusions or subjects treated with ESA during the study period. • Adverse events (AE): type, nature, incidence and outcome. • Time to transfusion/treatment with ESA. • Change in iron and haematology variables from baseline to Weeks 2, 4, 6, 8 (serum ferritin, TSAT, serum iron, endogenous erythropoietin (EPO), hepcidin and interleukin-6, blood reticulocyte Hb content). In addition, the following predefined efficacy variable was analysed: • The percentage of subjects with treatment response, defined as Hb increase of ≥1 g/dL or Hb ≥11 g/dL at any time during the study, in the absence of any RBC transfusion or ESA treatment.

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Primary and Secondary Efficacy Endpoints and Safety Criteria:	Safety Criteria: • AEs: type, nature, incidence, and outcome. • Clinical laboratory tests. • Physical examinations, vital signs, electrocardiograms (ECGs). • Changes in concomitant medications.
Procedures:	Screening Period: Duration of up to 4 weeks prior to first infusion (written informed consent, eligibility criteria, demographics, medical/surgical history, prior medication, Vitamin B_{12} level, folic acid level, serum haptoglobin level, physical examination, vital signs, ECG, iron status, and clinical laboratory parameters). Treatment/Follow-up Period: Duration of 8 weeks (Day 1 (Week 0)): baseline confirmation of eligibility, demographics, vital signs, physical examination, clinical laboratory tests, iron status; randomisation, and administration of study treatment (or no treatment); recording of AEs and concomitant medications). Visits for assessment of safety and efficacy every 2 weeks (±3 days) at Weeks 2, 4, 6, and 8. End of Study (or Early Discontinuation) Visit: Week 8 ± 3 days (physical examination, vital signs, ECG, iron status, and clinical laboratory variables, AEs, disease stage).
Sample Size:	Based on the assumptions of a standard deviation (SD) of 1.5 and a 1-sided alpha of 0.05, 20 subjects per group were considered to give a power of 68% to detect an expected difference of 1.0 g/dL in the Hb change from baseline to Weeks 4, 6 and 8. The expected difference of 1.0 g/dL and an SD of 1.5 was based on prior study data of FCM in other indications, publications relevant to this study population, and more recently supported by a large observational study using FCM in cancer subjects suffering from anaemia. These data from a large observational study in cancer subjects receiving 500-4,000 mg of FCM for treatment of iron-restricted erythropoiesis and anaemia showed a mean increase from baseline in Hb of 1.0 g/dL or greater by Week 4 with an SD of 1.3-1.6 g/dL. The sample size of 40 subjects was chosen based on feasibility and was considered sufficient for this pilot study. However, due to low recruitment, the Sponsor decided to stop recruitment on 31 October 2012 after 19 subjects were randomised. Thus, the power of the study is below the initial assumptions for the statistical analyses.

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Statistical Methods:	Efficacy Analyses: Three analysis populations were defined: the full analysis set (FAS; randomised subjects who received at least 1 dose of treatment (if in the FCM arm) and attended at least 1 post-baseline visit), the per-protocol population (PP; FAS subjects who had no major protocol deviations), and the safety population (all randomised subjects who received at least 1 dose of treatment or were randomised to the no treatment group). Analyses of the primary efficacy endpoint, the change in Hb from baseline to Weeks 4, 6, and 8, were performed on both the FAS and PP populations; analyses of the secondary endpoints were performed on the FAS population only. Analyses of the primary endpoint were conducted using mixed-effect model for repeated measures. Model terms included subject as a random effect, fixed effects of week, treatment, and treatment-by-week interaction, as well as baseline Hb value as a covariate. All tests based on proportions were to be done using exact logistic regression with an adjustment for the baseline Hb value; if logistic regression assumptions were violated, the test of homogeneity based on the chi-square distribution was to be used; or in the case of small expected frequencies, Fisher's exact test was to be used. Time-to-event analyses were investigated using Kaplan-Meier survival plots with the log-rank test being used to make comparisons. For all primary and secondary analyses, the significance level was set at an alpha of 0.05, and no adjustment was made for multiplicity. Safety Analyses: All AEs were classified using the Medical Dictionary for Regulatory Activities coding dictionary, Version 15.1. All AEs were listed by treatment group and subject. Treatment-emergent AEs (TEAEs) were summarised by system organ class, preferred term (PT), treatment group, and overall. Summaries by relationship to study treatment, severity, seriousness, and outcome of death were created. Prior, concomitant, and changes in concomitant medications were classified using the September 2012 version of the World Health Organization Drug Dictionary. The number and percentage of subjects taking each drug were summarised by Anatomical Therapeutic Chemical (ATC) level 1, ATC level 2, PT, treatment group, and overall. The number and percentage of subjects reporting post-baseline abnormal clinically significant results for physical examination, vital signs, laboratory evaluations, and ECG results were tabulated by treatment group.

Results:

Baseline Characteristics:

A total of 12 males and 7 females took part in the study; the mean age was 67.7 years, with a range of 26 to 88 years. More than half of the subjects were >66 kg with a mean weight of 69.84 kg and a range of 49.0 to 103.7 kg. The demographics were comparable between treatment groups.

For the primary tumour diagnoses, more than half of the subjects had MM (11/19 subjects), followed by indolent NHL (6/19 subjects) and CLL (2/19 subjects).

Exposure to Study Medication, Chemotherapy, and Concomitant Anaemia Treatments:

Eight subjects were randomised to Arm A to receive FCM administration; 5 subjects received 1 FCM administration (1,000 mg iron) as their weight was >66 kg, and 3 subjects received 2 FCM administrations (each 500 mg iron). All 8 subjects completed the study. In Arm B, 11 subjects were randomised, and 8 subjects completed the study; 2 subjects were randomised in error and were subsequently discontinued, and 1 subject withdrew consent. All subjects were receiving at least 1 type of cancer treatment: antineoplastic agents (18 subjects), corticosteroids for systemic use (13 subjects), immunosuppressants (2 subjects), and other therapeutic products (2 subjects). No subject received RBC transfusions or ESA treatments during the study.

Efficacy Results:

For the primary efficacy endpoint, the analyses were performed for the FAS population (17 subjects, with 8 subjects in Arm A and 9 subjects in Arm B) and for the PP population (12 subjects, with 5 subjects in Arm A and 7 subjects in Arm B). Secondary efficacy endpoints were performed for the FAS population only. As the Sponsor stopped the study after 19 subjects were enrolled due to low recruitment, the power of the study is below the initial assumptions (<68%) for the planned statistical analyses. Results of the treatment difference analyses are presented in the tables as planned, but any statistical significance claimed must be considered with caution based on the small sample size.

Primary Efficacy Conclusions:

- For the FAS population, the mean increases from baseline in the Hb level were greater in Arm A than in Arm B at Weeks 4, 6, and 8; the treatment difference (Arm A Hb level minus Arm B Hb level) was greatest and statistically significant at Week 8 (p=0.021). Therefore, the primary endpoint of this study was met at Week 8.
- For the PP population, the mean increases from baseline in the Hb level were greater in Arm A than in Arm B at Weeks 4, 6, and 8; the treatment difference was approximately the same and statistically significant at each of these time points (all $p \leq 0.005$).

Results:
(Cont'd)

Secondary Efficacy Conclusions:

- A total of 8 (100%) subjects in Arm A and 6 (66.7%) subjects in Arm B had Hb increases from baseline of ≥1 g/dL at some point during the study in the absence of any RBC transfusion or ESA treatment.
- The percentage of subjects who had Hb levels of ≥11 g/dL at any time during the study in the absence of any RBC transfusion or ESA treatment was higher in Arm A (7 (87.5%) subjects) than in Arm B (5 (55.6%) subjects).
- From the Kaplan-Meier estimates, the median time to Hb response was 2.29 weeks in Arm A and 4.44 weeks in Arm B. The minimum time to achieve Hb response was shorter in Arm A (0.57 weeks) than in Arm B (0.95 weeks). The estimated probability of achieving Hb response was higher in Arm A than in Arm B at each time point.
- No subject received an RBC transfusion or an ESA treatment during the study.
- The percentage of subjects who had a treatment response (Hb increase of ≥1 g/dL or Hb ≥11 g/dL at any time during the study in the absence of any RBC transfusion or ESA treatment) was higher in Arm A (8 (100%) subjects) than in Arm B (6 (66.7%) subjects).
- Greater mean increases from baseline in ferritin, TSAT, and serum iron were observed in Arm A compared to Arm B, with the greatest treatment differences at Weeks 2 and 4. Greater mean decreases from baseline in EPO were observed in Arm A compared to Arm B, with the greatest treatment difference at Week 2. Mean decreases from baseline in interleukin-6 were observed in both treatment arms, with slightly greater decreases in Arm B. Mean changes from baseline in reticulocyte Hb and hepcidin were similar in Arm A and Arm B.
- The percentage of subjects who had a treatment response (Hb increase of ≥1 g/dL or Hb ≥11 g/dL at any time during the study in the absence of any RBC transfusion or ESA treatment) was higher in Arm A (8 (100%) subjects) than in Arm B (6 (66.7%) subjects).

Safety Results:

In general, only 14 TEAEs were reported overall (12 in Arm A, 2 in Arm B) in a total of 6 subjects (5 in Arm A, 1 in Arm B). Given the elderly population included in this study with lymphoid malignancy, undergoing chemotherapy, this seems to reflect poor adherence to safety reporting. The open-label design with a "no treatment" group (Arm B) might have contributed to a bias in reporting of TEAEs. Therefore, interpretation of safety data has to be done with caution.

Results: (Cont'd)	Safety Results: (Cont'd) • Overall, FCM was generally well tolerated. There were no TEAEs leading to discontinuation of study treatment. Six subjects reported a total of 14 TEAEs (5 subjects reported 12 events in Arm A, and 1 subject reported 2 events in Arm B), and none of the TEAEs were considered related to study drug. The TEAEs were mild or moderate in intensity except for 1 severe event of injury in Subject 603-004, who was randomised to Arm A. The event of injury occurred 10 days after the end of study visit and was reported as a post-study serious adverse event (SAE); the subject fell down the stairs in alcohol intoxication, leading to multiple fractures, resulting in fatal multi-organ failure. During the study, this same subject had an SAE of atrial fibrillation that was ongoing at the end of study visit. Only 1 TEAE, herpes zoster, was reported in 2 subjects (both in Arm A); all other events were reported in 1 subject each. • For haematology parameters, mean increases from baseline were noted at each post-baseline visit in both treatment arms for haematocrit and erythrocyte mean corpuscular Hb, with greater mean increases in Arm A compared to Arm B. Small mean increases in erythrocyte mean corpuscular volume were observed in Arm A. There were no trends in the changes in neutrophils, platelets, or reticulocytes during the study. No subject in Arm A had a clinically significant change post-baseline in any of the haematology parameters. In Arm B, clinically significant changes compared to screening/baseline were reported during the study but were within normal ranges: 3 subjects had clinically significant changes in Hb values, 2 subjects in haematocrit values, and 1 subject each had a change in iron value and reticulocyte Hb value. No laboratory change was reported as a TEAE during the study. • For biochemistry parameters, mean decreases from baseline in C-reactive protein were observed at post-baseline visits in both treatment arms, with greater mean decreases in Arm B. There were no trends in the changes in other biochemistry parameters during the study. No subject in Arm A had a clinically significant change post-baseline in any of the biochemistry parameters. In Arm B, 1 subject had an increased C-reactive protein value at Week 2 (171.5 mg/L, normal range: 0 to 200 mg/L) compared to screening (21 mg/L). • No subject was reported to have a clinically significant change in any of the vital signs parameters or physical examination findings post-baseline. One subject (in Arm A) had a post-baseline change in ECG results that was clinically significant; at Week 8, the subject had clinically significant signs of ventricular hypertrophy not observed at screening.