SYNOPSIS

FER-AOC-MM

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 multiple myeloma and iron-restricted erythropoiesis receiving chemotherapy (FER-AOC-MM)
Recruiting Investigators:	Dr. Olivier Decaux, Rennes, France Dr. Eurydiki Michalis, Athens, Greece Dr. Meletios Athanasios Demopoulos, Athens, Greece
Study Sites :	Hôpital Sud, Service de médecine Interne, Rennes, France; Gennimatas General Hospital of Athens, Hematology Department, Athens, Greece; Alexandra Hospital, Department of Therapeutics, Oncology Unit, Athens, Greece..
Indication:	Newly diagnosed or recurrent multiple myeloma subjects scheduled to receive chemotherapy with anaemia and iron-restricted erythropoiesis
Studied Period (years) 30NOV2010 01JUN2011	Phase of development: 3b
Objectives:	Primary Objective: • To evaluate the efficacy of FCM given without erythropoiesis-stimulating agents (ESA) in the correction of haemoglobin (Hb) levels in subjects with multiple myeloma (MM) 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 MM subjects
Design:	This was a prospective, multicentre, randomised, controlled, 2-arm, open-label pilot study to evaluate efficacy and safety of FCM in the treatment of anaemia in subjects with MM initiating chemotherapy. Eligible subjects were randomised (1:1) to receive either 1000 mg iron as FCM as an intravenous (IV) infusion or standard of care (the subjects were allowed to be treated according to the local institutional practice if required for symptomatic management of anaemia). All subjects were to be followed up for 8 weeks after randomisation.

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	Forty subjects were planned to be included in this study. However, due to low recruitment, Vifor decided to terminate the study prematurely after 3 subjects were randomised. As a result, only the safety results of these 3 subjects are discussed.
Treatment:	Arm A: After randomisation, subjects were to receive a total dose of 1000 mg iron as FCM on the day of the first scheduled chemotherapy cycle or within 24 hours before or after receiving chemotherapy. In subjects weighing ≤66 kg, the first dose (500 mg) was to be administered on the day of the first scheduled chemotherapy cycle (Day 1) and the second dose (500 mg) at the next study visit (Week 2; Day 14 ± 3 days). If a subject had an elevated transferrin saturation (TSAT) level (>50%) or elevated ferritin level (>600 ng/mL), an elevation of liver enzymes over 3 times the upper limit of normal, or a transfusion since the first dose of FCM, then the second dose was to be withheld at Week 2; if the values were within the specified ranges at Week 4, then the second dose could be given. 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.
Number of Patients	Planned: 40 Analyzed: 3
Test product	Ferric carboxymaltose (Ferinject®), 1000 mg, intravenous application. Batch Nr. 882200
Inclusion Criteria:	1. Subjects (male or female) aged ≥18, suffering from a newly diagnosed or progressed/relapsed MM and scheduled to receive anti-myeloma treatment. Progression was defined according to "Uniform Response Criteria for Multiple Myeloma". 2. Subjects with progressed/relapsed MM should have had stable disease during the last 3 months since prior treatment. Note: Subjects on a maintenance therapy with lenalidomide (with or without dexamethasone) for at least 3 months who progressed and required further anti-myeloma therapy were also permitted to be enrolled in the study. 3. Life expectancy of at least 6 months. 4. 8.5 g/dL ≤ Hb ≤11 g/dL at the time of randomisation. 5. Iron-restricted erythropoiesis defined as:

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	• Stainable iron in bone marrow (BM) combined with TSAT ≤20%, or • If the evaluation of stainable iron in BM was not possible or available: ▪ Ferritin >30 ng/mL (women) or >40 ng/mL (men), and ▪ TSAT ≤20% 6. Females of child-bearing potential must have had a negative urine pregnancy test at screening. 7. Before any study-specific procedure, the appropriate written informed consent (IC) must have been obtained.
Exclusion Criteria:	1. Any anaemia treatment within 4 weeks prior to randomisation (including red blood cell (RBC) transfusions, treatment with ESA, or any oral/parenteral iron preparations). 2. Anthracycline-containing chemotherapy regimens. 3. Subjects weighing <35 kg. 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. Known chronic renal failure, glomerular filtration rate <30 mL/min/m^2. 7. Recent (within last 4 weeks) significant bleeding/surgery, defined as drop in Hb of ≥2 g/dL. 8. Clinically relevant active inflammatory disease other than MM (according to the judgment of the investigator). 9. Clinically relevant ongoing infectious disease including known human immunodeficiency virus. 10. Serum ferritin >600 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 New York Heart Association Grade III or IV at screening, or poorly controlled hypertension at screening according to the judgment of the investigator. 13. Elevation of liver enzymes (aspartate aminotransferase, alanine aminotransferase) over 3 times above the normal range or known acute hepatic disorder.

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	14. Subject currently enrolled in or did not complete at least 30 days since ending other investigational device or drug study(ies), or subject received other investigational agent(s). 15. 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 IC and/or to comply with study procedures
Primary and Secondary Endpoints:	<u>Primary Endpoint</u>: • Mean change in Hb from baseline to Weeks 4, 6, and 8 (end of study) in the absence of any red cell transfusion or ESA treatment. <u>Secondary Endpoints</u>: • The percentage of subjects with blood Hb response of at least 1 g/dL at any study week in the absence of any red cell transfusion or ESA treatment. • The percentage of subjects with an Hb correction to at least 12 g/dL in the absence of any red cell transfusion or ESA treatment. • The median time to Hb response defined as an increase in Hb of at least 1 g/dL in the absence of any red cell transfusion or ESA treatment. • The proportion of subjects receiving RBC transfusions or subjects treated with ESA during the study period. • Adverse events: 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), blood reticulocyte Hb content/RBC size factor, percentage of hypochromic red cells/percentage of low Hb density, hepcidin, and interleukin-6).

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Procedures:	Screening Period: Up to 4 weeks (written IC, eligibility criteria, demographics, medical/surgical history, prior medication, Vitamin B_{12} level, folic acid level, serum haptoglobin level, physical examination, vital signs, electrocardiogram [ECG], iron status, and clinical laboratory parameters). Treatment Period: 8 weeks (administration of study medication on Day 0, physical examination, vital signs, iron status, and clinical laboratory variables). Assessment visits every 2 weeks (±3 days). End of Study (or Early Discontinuation): Week 8 ± 3 days (physical examination, vital signs, ECG, iron status and clinical laboratory variables, adverse events [AEs], disease stage).
Sample Size:	Based on the assumptions of a standard deviation of 1.5 and a one-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. The sample size (40 subjects) was chosen based on feasibility and was considered sufficient for this pilot study. Due to low recruitment, the study was stopped early. Therefore, no statistical comparison between FCM and the comparator (no treatment) was performed.
Statistical Methods:	No summary tables or statistical analyses were performed as the study was stopped early, and too few subjects were randomised for analysis. All electronic case report form (eCRF) data collected were presented within by-subject data listings. The data listings were sorted by treatment group, centre number, subject number, and visit. Any data collected on subjects who were subsequently not randomised were presented within a non-randomised group.
Results:	The study was prematurely terminated by Vifor on 30 April 2011. The captured data for the 3 randomised subjects from 3 different sites (2 in Greece and 1 in France) are presented in by-subject listings. Primary and secondary efficacy variables were not derived, and no summary or statistical analysis tables were produced. Baseline Characteristics Of the 7 subjects screened, 4 were screen failures, and 3 were randomised: 2 subjects were randomised to Arm A (FCM group), and 1 subject to Arm B (no treatment group). All 3 randomised subjects completed the study. None of the 3 randomised subjects had received previous anti-anaemia treatments. Exposure to Study Medication, Chemotherapy, and Concomitant Anaemia Treatments Both subjects randomised to Arm A were ≤66 kg, and each of them received 1000 mg iron as FCM in 2 doses of 500 mg.

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	Subject 101-001 (FCM group) received 3rd line of therapy as bortezomib and dexamethasone, plus radiotherapy, starting on 28 December 2010 (received therapy during Weeks 0, 1, 3, 4, 6, and 7). The subject received doses of FCM 500 mg on 28 December 2010 (Week 0) and 25 January 2011 (Week 4). In addition to the study medication to treat anaemia, the subject received darbepoetin alfa subcutaneously once a week from Week 1 to Week 4 (03 January 2011 to 25 January 2011), and oral ferrous sulphate twice daily from Week 0 to Week 4 (31 December 2010 to 21 January 2011). Subject 204-001 (FCM group) received 1st line of therapy as melphalan and dexamethasone starting on 08 April 2011 (no subsequent dates of chemotherapy were recorded), with concomitant subcutaneous pegfilgrastim after 4 days of chemotherapy (12 April 2011, Week 0) for neutropenia treatment. The subject received 2 doses of FCM 500 mg on 08 April 2011 and 19 April 2011, and no other anti-anaemia treatment. Also, the subject received a zoledronic acid injection 4 mg IV for treating bone disease at Week 6 (12 May 2011). Subject 203-001 (no treatment group) received 4th or greater line of therapy as cyclophosphamide in combination with an "other" chemotherapy agent (details not provided) starting on 28 March 2011 (no subsequent dates of chemotherapy were recorded). To treat anaemia, the subject received darbepoetin alfa subcutaneously once a week starting at Week 2 (12 April 2011) and ongoing at the final study visit, and infusions of RBCs at Week 4 (1 pack was received on 26 April 2011), Week 6 (2 packs were received on 10 May 2011), and Week 8 (1 pack was received on 31 May 2011). <u>Adverse Events</u> There were no deaths, serious AEs (SAEs), or treatment-related AEs reported by the 3 randomised subjects in this study. Overall, the 3 subjects reported a total of 10 AEs. In the subjects treated with FCM, the following AEs were reported: asthenia, confusional state, eye inflammation, increased C-reactive protein (CRP), and urinary tract infection. In the no treatment group, peripheral oedema, fatigue, anaemia, and gingival bleeding (2 episodes) were reported. The AEs were mild or moderate in intensity except for 1 severe event of peripheral oedema. None of the AEs was considered related to study drug. <u>Laboratory Parameters</u> In 2 subjects in Arm A, after administration of FCM, an increase in Hb levels from baseline to most follow-up visits was observed in both subjects (see the following table). In Subject 203-001 in Arm B (no treatment group), a decrease in Hb levels was observed at Weeks 2, 4, and 6.

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Haemoglobin Level (g/dL)					
Subject Number (Treatment Group)	**Baseline (Week 0)**	**Week 2**	**Week 4**	**Week 6**	**Week 8**
101-001 (FCM)	9.7	10.6	12.9	12.8	12.9
204-001 (FCM)	9.0	10.2	10.0	9.1	8.8
203-001 (No treatment)	8.8	8.0	7.4	7.4	8.4

In addition to study treatment (FCM 500 mg at Weeks 0 and 4), Subject 101-001 received oral ferrous sulphate twice daily from Week 0 to Week 4, and darbepoetin alfa subcutaneously once a week from Week 1 to Week 4. Subject 204-001 received only the study treatment for treating anaemia.

Subject 203-001 in Arm B received rescue anaemia treatment, including darbepoetin alfa subcutaneously once a week from Week 2 (ongoing at the final study visit) and transfusions of RBCs at Weeks 4, 6, and 8.

In both subjects in the FCM group, serum ferritin increased above the upper limit of normal after treatment with FCM (see the following table); there were no AEs reported with regard to these high values. Of note, Subject 101-001 had an AE of increased CRP, 3 weeks after baseline, and Subject 204-001 had an ongoing urinary tract infection during the study, with an increased CRP level compared to baseline at Week 6. Infection and inflammation might have led to an increase in serum ferritin, which is an acute phase reactant.

Ferritin Level (ng/mL)					
Subject Number (Treatment Group)	**Baseline (Week 0)**	**Week 2**	**Week 4**	**Week 6**	**Week 8**
101-001 (FCM)	45	1296	234	548	750
204-001 (FCM)	445	1176	1897	2235	1861
203-001 (No treatment)	ND	113	ND	ND	ND

ND=not done

For TSAT values, Subject 204-001 (FCM group) had increased values compared to baseline at all follow-up visits, including an abnormally elevated TSAT level (>50%) at Week 2 (see the following table).

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Transferrin Saturation (%)					
Subject Number (Treatment Group)	**Baseline (Week 0)**	**Week 2**	**Week 4**	**Week 6**	**Week 8**
101-001 (FCM)	15.4	26.4	10.4	16.4	14.8
204-001 (FCM)	8.0	52.2	24.2	18.9	38.4
203-001 (No treatment)	16.2	15.6	15.8	31.4	30.4

Serum iron values are shown in the following table.

Serum Iron (µmol/L)					
Subject Number (Treatment Group)	**Baseline (Week 0)**	**Week 2**	**Week 4**	**Week 6**	**Week 8**
101-001 (FCM)	10.8	17.8	7	9.4	8.5
204-001 (FCM)	0.3	20.1	7.0	4.1	17.7
203-001 (No treatment)	ND	ND	ND	ND	ND

ND=not done

Other Safety Parameters

No clinically significant changes were noted in any of the vital signs parameters at screening. One new clinically significant abnormal ECG (ventricular rhythm disturbance) was noted at Week 8 in comparison to results at screening in Subject 204-001 (FCM group). This was considered unrelated to study drug.

Conclusions:	Due to the limited number of subjects included in this study, no safety or efficacy conclusions can be drawn. Two FCM-treated subjects, 1 of whom concurrently received darbopoietin alpha, demonstrated an increase from baseline in Hb over the course of the study without the use of transfusions. FCM did not cause a safety concern in these elderly subjects with advanced MM undergoing chemotherapy, and seemed to be well tolerated.