CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 203565/0
Drug Name:	Ferric Carboxymaltose
Indication(s):	Iron Deficiency Anemia
Applicant:	Luitpold Pharmaceuticals, Inc.
Date(s):	Stamp Date: 10/3/2011
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Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Kyung Yul Lee, Ph.D., Statistical Reviewer
Concurring Reviewers:	Mark Rothmann, Ph.D., Lead Mathematical Statistician
	Tomas Gwise, Ph.D., Division Deputy Director
Medical Division:	Division of Hematology Products
Clinical Team:	Dr. Min Lu, Clinical Reviewer
	Dr. Kathy Robie Suh, Clinical Team Leader
Project Manager:	Ms. Baird

Keywords:
Iron deficiency anemia, impaired renal function, hemoglobin, noninferiority test, ANCOVA,

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1. EXECUTIVE SUMMARY

This submission consists of the results of two studies, 1VIT9030 and 1VIT9031. Study 1VIT9030 was a multicenter, randomized, active-controlled, open-label study that compared the safety and efficacy of intravenous (IV) Ferric carboxymaltose (FCM) versus IV Venofer in subjects who had iron deficiency anemia (IDA) and impaired renal function. Study 1VIT9031 was a multicenter, randomized, active-controlled study to compare the efficacy and safety of FCM in subjects who had IDA in two cohorts. Cohort 1 included oral iron subjects who had an unsatisfactory response to a 14-day oral iron run-in and Cohort 2 included subjects who were poorly tolerant or otherwise inappropriate for oral iron. The dose and schedule for these phase III trials was FCM 15 mg/kg to a maximum of 750 mg per dose on Days 0 and 7 for a total maximum dose of 1500 mg. These two studies were conducted in the United States.

The observed mean changes in hemoglobin from baseline to the highest values during the study period demonstrated clinical benefit in subjects who had iron deficiency anemia impaired renal function with non-dialysis dependent chronic kidney disease (CKD) (1VIT9030) and oral iron subjects who had an unsatisfactory response to a 14-day oral iron run-in (1VIT9031).

The key statistical issues and findings are as follows:

- For Study 1VIT9030, the estimated mean difference between FCM and Venofer was 0.21 g/dL with 95% CI of (0.13, 0.28). FCM was noninferior to Venofer in mean change in hemoglobin with the lower limit (0.13) of the 95% CI above the noninferiority margin of -0.2 g/dL. FCM was even statistically superior to Venofer on the mean change in hemoglobin from baseline to the highest value during the study period.

- The primary composite safety endpoint in the Study 1VIT9030 was the proportion of subjects experiencing the primary composite safety endpoint of death, nonfatal myocardial infarction, nonfatal stroke, unstable angina requiring hospitalization, congestive heart failure, arrhythmias, protocol-defined hypertensive and hypotensive events. A total of 175 subjects (13.7%) in FCM and 156 subjects (12.2%) in Venofer had one or more composite safety events with 95 % CI of (-1.1, 4.3). The most common event among the primary composite safety endpoint was protocol-defined hypertensive events, 7.5% subjects in FCM and 4.4% subjects in Venofer, respectively. After excluding protocol-defined hypertensive and hypotensive events, 5.5% subjects in FCM and 5.4% subjects in Venofer had events. Death, nonfatal myocardial infarction or nonfatal stroke events were observed 1.9% subjects in FCM and 2.7% subjects in Venofer.

- For the proportion of subjects with an increase in hemoglobin $\geq$ 1.0 g/dL from baseline to the end of study period, subjects in FCM not only demonstrated noninferiority with lower bound of 3.6 % above noninferiority margin of -7.5%, but also demonstrated superiority with 95% CI of (3.6, 11.5) compared to that of Venofer in study 1VIT9030.

- For Study 1VIT9030, the mean increases in ferritin, total transferring saturation (TSAT), and serum iron and mean decreases in total iron building capacity (TIBC) and unsaturated iron building capacity (IBC) from baseline to the highest value from baseline to the end of study period were statistically significantly greater in the FCM subjects than in the Venofer subjects.

- For study 1VIT9031, subjects in FCM demonstrated superiority to Oral Iron in Cohort 1 which included oral iron subjects who had an unsatisfactory response to a 14-day oral iron run-in with an estimated difference between FCM and oral iron of 0.76 g/dL and 95% CI of (0.59, 0.93) (P<0.0001) with respect to the mean change in hemoglobin from baseline to the highest value between baseline and Day 35 (or time of intervention) after adjusting for etiology.

- For study 1VIT9031, all supportive efficacy endpoints for Cohort 1 and Cohort 2 were superior for subjects in the FCM arm compared to subjects in the oral Iron arm in Cohort 1. Similar finding applied to the IV SC arm in Cohort 2.

2. INTRODUCTION

2.1 Overview

Ferric carboxymaltose (FCM) is a Type I polynuclear iron (III)-hydroxide carbohydrate complex being developed as a parenteral iron replacement therapy for the treatment of iron-deficiency anemia (IDA).

In the Drug Safety and Risk Management advisory meeting held February 01, 2008 for the previously submitted New Drug Application (NDA), FDA advisory committee members advised to reduce the maximum individual dose of FCM for the original NDA that was the maximum of 1,000 mg per infusion with a total maximum cumulative dose of 2,500 mg over 3 infusions.

Luitpold Pharmaceuticals, Inc. designed and conducted these two additional phase 3, open-label, randomized, multicenter, active controlled studies to assess the safety and efficacy collaborated with the (b) (4). The FCM was administered with a maximum individual dose of 750 mg each with a total maximum cumulative dose of 1,500 mg over 2 infusions in these two studies (1VIT09031 and 1VIT09030). At the May 18, 2009 meeting, it was discussed that two large studies of 1VIT9030 and 1VIT9031 would be the main studies and the results of these two trials would be taken in the context of the totality of the data available for evaluating the safety and efficacy of FCM. Both studies included the composite cardiovascular safety endpoint that was independently adjudicated by the Clinical Events Classification (CEC) committee of (b) (4).

The primary objective of Study 1VIT9030 was to estimate the cardiovascular safety and efficacy of an investigational IV FCM compared to IV Venofer in subjects who had IDA and impaired

renal function with non-dialysis dependent chronic kidney disease (CKD) at elevated risk of cardiovascular disease. A total of 2584 subjects were randomized (187 sites in the U.S); 1290 subjects into FCM and 1294 subjects into Venofer. Subjects were administered FCM 15 mg/kg to a maximum of 750 mg per dose on Days 0 and 7 for a total maximum dose of 1500 mg or Venofer 200 mg on Days 0, 7, and 14 with 2 additional doses between Days 0 and 7 and between Days 7 and 14 for a total of 5 doses (1000 mg). The primary efficacy endpoint was the mean change from baseline to the highest observed hemoglobin (Hgb) any time from baseline to Day 56 (or time of intervention). The composite safety endpoint included death due to any cause, nonfatal myocardial infarction, nonfatal stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization or medical intervention, arrhythmias, hypertension, or hypotension.

The primary objective of Study 1VIT9031 was to demonstrate the efficacy and safety of an investigational IV FCM for subjects with IDA due to a variety of etiologies (unsatisfactory response, intolerability or side effects) to fail a 14-day run-in course of oral iron before randomization to FCM or continuation of oral iron and subjects who did not tolerate oral iron or who were deemed unsuitable by the Investigator for the oral iron lead-in. Cohort 1 included oral iron subjects who had an unsatisfactory response to a 14-day oral iron run-in. Subjects were randomized in a 1:1 ratio to receive either IV FCM 15 mg/kg to a maximum dose of 750 mg per dose on Days 0 and 7 for a total maximum dose of 1500 mg (Group A) or continuation of oral iron ferrouts sulfate 325 mg PO, TID for an additional 14 days (Group B). Cohort 2 included subjects who were poorly tolerant or otherwise inappropriate for oral iron. Subjects were randomized in a 1:1 ratio to receive either IV FCM (same dose with Group A) or IV standard care (SC) (other IV iron) as determined by the study site physician. A total of 997 subjects were randomized (84 sites in the U.S.); 246 subjects in Group A (FCM), 253 subjects in Group B (oral iron) in Cohort 1 and 253 subjects in Group C and 245 subjects in Group D in Cohort 2. The primary endpoint is the mean change from baseline to the highest observed hemoglobin any time between baseline and Day 35 (or time of intervention) in Cohort 1. The composite endpoint was the same with Study 1VIT9030.

Table 1 : List of all studies included in analysis

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
1VIT9030	Phase 3	Up to Day 56 (additional up to 3 months)	1 month	Randomized FCM:1290 Venofer: 1294	Iron deficiency anemia
1VIT9031	Phase 3	Up to Day 35	1 month	Randomized Cohort 1 FCM: 246 Oral Iron: 253 Cohort 2 FCM: 253 IV SC: 245	unsatisfactory response to a 14-day oral iron run-in (Cohort 1) intolerant or unsuitable of oral iron (by investigator) during the run-in (Cohort 2)

2.2 Data Sources

Data and study reports were provided electronically, the location/names of data sets are as follows;
Study reports:
\\Cdsesub1\evsprod\NDA203565\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\iron-def-anemia\5351-stud-rep-contr\1vit09030
\\Cdsesub1\evsprod\NDA203565\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\iron-def-anemia\5351-stud-rep-contr\1vit09031

Data sets
\\Cdsesub1\evsprod\NDA203565\0000\m5\datasets\1vit09030
\\Cdsesub1\evsprod\NDA203565\0000\m5\datasets\1vit09031

The "raw" and derived datasets were submitted, and the SAS programs were submitted.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Review the quality and integrity of the submitted data.

- It was possible to reproduce the primary analysis dataset from tabulation or "raw" datasets.
- It was possible to trace how the primary endpoint was derived from the original data source (e.g., case report form).

3.2 Evaluation of Efficacy

3.2.1 1VIT9030

Study Design and Endpoints

Study Design
Study 1VIT9030 was multicenter, randomized, active-controlled, open-label study that compared the safety and efficacy of IV FCM versus IV Venofer in subjects who had IDA and impaired renal function. Subjects must have had a hemoglobin ≤11.5 g/dL (based on the mean of 2 values determined by central laboratories drawn within 7 days; the two values being within 0.7 mg/dL of each other) and chronically impaired renal function as defined by either of the following:

1. Glomerular filtration rate (GFR) <60 ml/min/1.73 m² on two measurements during the screening period (using the Modification of Diet in Renal Disease [MDRD] calculation), or
2. GFR <90 ml/min/1.73 m² on two measurements during the screening period and either one or both of the following:

- Kidney damage as indicated by abnormalities in composition of urine (as documented in the subject's medical history)
- Elevated risk of cardiovascular disease (Category 2 or 3) based on the Framingham Model

The stratification factors were baseline hemoglobin (≤9, 9.1 to 10.0, >10.1 g/dL), baseline cardiovascular risk (history of myocardial infarction, stroke, or congestive heart failure [yes/no]), erythropoietin use (yes/no), and CKD stage as per K/DOQI stage of CKD (2, 3-4, or 5). During the Treatment Phase, the FCM Group received two doses of FCM at 15 mg/kg to a maximum of 750 mg per dose for a maximum total dose of 1,500 mg. The Venofer Group received 5 doses of Venofer, 200 mg for a total dose of 1,000 mg.

Endpoints

The **primary efficacy endpoint** was the mean change from baseline to the highest observed hemoglobin any time between baseline and end of treatment period (Day 56) (or time of intervention).

Other supportive efficacy endpoints were as follows;

- Proportion of subjects achieving an increase in hemoglobin of ≥1 g/dL any time between baseline and end of treatment period (Day 56) (or time of intervention)
- Mean change from baseline to the highest observed ferritin any time between baseline and treatment period (Day 56) (or time of intervention)
- Mean change from baseline to the highest observed TSAT any time between baseline and treatment period (Day 56) (or time of intervention)
- Mean change from baseline to the pre-dosing value on Day 7 for hemoglobin, ferritin, and TSAT

The hematologic parameters were to be measured on screening phase (days -14 and -1), days 7, 14, 28 and 56 on treatment phase and days between 57 and 90 on the extra dose visit.

The **primary safety endpoint** was the proportion of subjects experiencing at least one treatment-emergent adverse event included in the primary composite safety endpoint. Treatment-emergent events included events that start on or after the first dose of randomized treatment. The composite safety endpoints which were adjudicated by the Clinical Events Classification (CES) committee of (b) (4) include:

- Death due to any cause
- Nonfatal myocardial infarction
- Nonfatal stroke
- Unstable angina requiring hospitalization
- Congestive heart failure requiring hospitalization or medical intervention
- Arrhythmias
- Hypertension
- Hypotension

Patient Disposition, Demographic and Baseline Characteristics

Sample size determination: This study enrolled a population with a high risk of cardiovascular events. Based on a comparison to the CHOIR database (data on file at (b) (4)) as well as the

Applicant's Phase 3 database for FCM, approximately 4% of subjects were expected to experience one or more of the events comprising the primary composite endpoint. The difference between FCM and Venofer in the proportion of subjects experiencing the primary composite endpoint was assessed with a 95% 2-sided CI constructed with the normal approximation to the binomial with continuity correction.

The planned sample size of 1250 per group was calculated providing evidence of equivalent cardiovascular risk for FCM and Venofer if the 95% CI included zero. This sample size provided >95% power to demonstrate noninferiority with a noninferiority margin of 0.2g/dL using 95% 2-sided CI for the difference between FCM and Venofer in the mean increase from baseline to the highest observed hemoglobin any time between baseline and end of study (or time of intervention).

In Study 1VIT04004, the observed mean difference between FCM and oral iron for the mean increase from baseline to the highest hemoglobin between baseline and Day 56 was 0.5 g/dL. In Study 1VEN03027, Venofer 1,000 mg IV in divided doses over a 14-day period was compared to oral iron. The observed mean difference for the increase from baseline to Day 56 was 0.4 g/dL. A patient-level standard deviation of 1.0 g/dL was estimated from these two studies.

Assuming that the difference between Venofer and placebo exceeded the difference of 0.4 g/dL for IV iron versus oral iron, a non-inferiority margin of 0.2 g/dL was chosen as the difference from placebo.

Of a total of 2584 subjects, 1290 subjects and 1294 subjects were randomized to FCM or Venofer, respectively, from 187 centers in the United States. Among 2584 subjects, 14 FCM and 9 Venofer randomized subjects were discontinued from the study prior to dosing due to subject's request or selection criteria/study compliance reasons. A total of 1276 subjects were treated in the FCM group and 1285 subjects were treated in the Venofer group. The patient disposition is summarized for the treated population in Table 2.

Table 2 : Patient Disposition: Treated Population (Study 1VIT9030)

Subjects Treated	FCM (N=1276)	Venofer (N=1285)	Total (N=2584)
Completed Treatment Phase (Screening – Day 56)	1048 (82.1%)	1042 (81.1%)	2090 (81.6%)
Not Complete Treatment Phase (Screening – Day 56)	228 (17.9%)	243 (18.9%)	471 (18.4%)
Adverse event	20 (1.6%)	22 (1.7%)	42 (1.6%)
Selection criteria/compliance	181 (14.2%)	188 (14.6%)	369 (14.4%)
Lost to follow-up	11 (0.9%)	10 (0.8%)	21 (0.8%)
Subject request	9 (0.7%)	17 (1.3%)	26 (1.0%)
Physician decision	3 (0.2%)	2 (0.2%)	5 (0.2%)
Other	4 (0.3%)	4 (0.3%)	8 (0.3%)

Completed Study Period (Screening – Day 120)	1059 (83.0%)	1073 (83.5%)	2132 (83.2%)
Not Complete Study Period (Screening – Day 120)	217 (17.0%)	212 (16.5%)	429 (16.8%)
Adverse event	35 (2.7%)	30 (2.3%)	65 (2.5%)
Selection criteria/compliance	138 (10.8%)	131 (10.2%)	269 (10.5%)
Lost to follow-up	23 (1.8%)	23 (1.8%)	46 (1.8%)
Subject request	17 (1.3%)	22 (1.7%)	39 (1.5%)
Physician decision	2 (0.2%)	1 (0.1%)	3 (0.1%)
Other	2 (0.2%)	5 (0.4%)	7 (0.3%)

A total of 1048 subjects (82.1%) in FCM and 1042 subjects (81.1%) in Venofer completed the Treatment Phase as scheduled (Screening –Day 56). Among 228 subjects who did not complete the Treatment Phase in FCM; 181 discontinued due to selection criteria/compliance, 20 discontinued due to adverse events, 11 were lost to follow-up, 9 discontinued due to subject's request, 4 discontinued for "other" reasons, and 3 discontinued due to physician decision. Among 243 subjects who did not complete the Treatment Phase as scheduled in Venofer; 188 discontinued due to selection criteria/compliance, 22 discontinued due to adverse events, 17 discontinued due to subject's request, 10 were lost to follow-up, 4 discontinued for "other" reasons, and 2 discontinued due to physician decision.

A total of 1059 (83.0%) subjects in FCM and 1073 subjects (83.5%) in Venofer completed the study as scheduled (Screening – Day 120). Among 217 subjects who did not complete the study as scheduled in FCM; 138 discontinued due to compliance, 35 discontinued due to adverse events, 23 were lost to follow-up, 17 discontinued due to subject's request, 2 discontinued for "other" reasons, and 2 discontinued due to physician decision. Among 212 subjects who did not complete the study as scheduled in Venofer; 131 discontinued due to selection criteria/compliance, 30 discontinued due to adverse events, 23 were lost to follow-up, 22 discontinued due to subject request, 5 discontinued for "other" reasons, and 1 discontinued due to physician decision.

The total number of subjects who completed the study period was greater than the total number of subjects who completed the treatment period because of two different completion criteria. A subject completed the treatment phase had to have received a dose of FCM or Venofer and completed the Day 56 Visit. A subject completed the study period needed to have at least one dose of FCM or Venofer and a safety follow-up on Days 120-125.

The efficacy evaluation population was modified intent-to-treat (ITT) population who received at least one dose of randomized study medication, had at least one post-baseline hemoglobin assessment, and had a stable (± 20%) erythropoiesis stimulating agent (ESA) for four weeks, which may include a dose of zero, before randomization.

The number of subjects in the safety and mITT populations is summarized in Table 3.

Table 3 : Number of subjects in Treated and mITT Populations (Study 1VIT9030)

	FCM	Venofer	Total
Randomized subjects	1290	1294	2584
No treatment	14	9	23
Treated population	1276	1285	2561
No post-baseline	23	33	56
No stable ESA	6	8	14
mITT population	1249*	1244	2493

* Two subjects had no post baseline and no stable ESA.

There were 2493 subjects in the mITT population, 1249 subjects on FCM and 1244 subjects on Venofer.

Demographic characteristics are summarized for the treated population in Table 4.

Table 4 : Demographic Characteristics: Treated Population (Study 1VIT9030)

	FCM (N=1276) n (%)	Venofer (N=1285) n (%)	Total (N=2561) n (%)
Age (years)			
Mean (SD)	67.5 (13.0)	67.2 (13.0)	67.3 (13.0)
≤ 65	500 (39.2)	536 (41.7)	1036 (40.5)
66-75	395 (31.0)	394 (30.7)	789 (30.8)
≥ 76	381 (29.9)	355 (27.6)	736 (28.7)
Sex			
Female	810 (63.5)	818 (63.7)	1628 (63.6)
Male	466 (36.5)	467 (36.3)	933 (36.4)
Race			
African American	334 (26.2)	325 (25.3)	659 (25.7)
Asian	20 (1.6)	21 (1.6)	41 (1.6)
Caucasian	676 (53.0)	693 (53.9)	1369 (53.5)
Hispanic	234 (18.3)	236 (18.4)	470 (18.4)
Other	12 (0.9)	10 (0.8)	22 (0.9)
Weight (kg) n	1275	1285	2560
Mean (SD)	89.6 (24.8)	89.7 (24.8)	89.7 (24.8)
BMI (kg/m²) n	1273	1285	2558
Mean (SD)	32.6 (8.7)	32.6 (8.6)	32.6 (8.6)

Mean age was 67.3 years; 67.5 years in FCM and 67.2 years in Venofer, respectively. Subjects' age > 65 years (FCM: 60.9%; Venofer: 58.3%) were the majority. Approximately, 64% of subjects in the safety population were female, and over 53.5 % of the subjects were Caucasian.

The baseline characteristics for the treated population are summarized in Table 5.

Table 5 : Baseline Characteristics: Treated Population (Study 1VIT9030)

	FCM (N=1276) n (%)	Venofer (N=1285) n (%)	Total (N=2561) n (%)
Baseline Hgb (g/dL)			
Mean (SD)	10.3 (0.8)	10.3 (0.8)	10.3 (0.8)
<=9.0 g/dL	103 (8.1)	102 (7.9)	205 (8.0)
9.1-10.0 g/dL	286 (22.4)	292 (22.7)	578 (22.6)
>=10.1 g/dL	887 (69.5)	891 (69.3)	1778 (69.4)
Baseline ferritin (ng/mL)			
Mean (SD)	73.0 (64.6)	75.1 (64.1)	74.0 (64.4)
Baseline TSAT (%)			
Mean (SD)	19.8 (7.8)	19.6 (7.4)	19.7 (7.6)
Baseline GFR-MDRD			
Mean (SD)	32.5 (14.7)	32.3 (14.9)	32.4 (14.8)
Erythropoietin Use			
No	1046 (82.0)	1057 (82.3)	2103 (82.1)
Yes	230 (18.0)	228 (17.7)	458 (17.9)
CKD stage			
2	68 (5.3)	78 (6.1)	146 (5.7)
3-4	1113 (87.2)	1105 (86.0)	2218 (86.6)
5	95 (7.4)	102 (7.9)	197 (7.7)
History of MI			
No	1079 (84.6)	1101 (85.7)	2180 (85.1)
Yes	197 (15.4)	184 (14.3)	381 (14.9)
History of Stroke			
No	1111 (87.1)	1128 (87.8)	2239 (87.4)
Yes	165 (12.9)	157 (12.2)	322 (12.6)
History of Congestive Heart Failure			
No	961 (75.3)	976 (76.0)	1937 (75.6)
Yes	315 (24.7)	309 (24.0)	624 (24.4)
Previous Iron Therapy			
No	580 (45.5)	592 (46.1)	1172 (45.8)
Yes	696 (54.5)	693 (53.9)	1389 (54.2)
History of Iron Intolerance			
No	1209 (94.7)	1222 (95.1)	2431 (94.9)
Yes	67 (5.3)	63 (4.9)	130 (5.1)

Mean hemoglobin, ferritin, and TSAT values at baseline were well balanced between FCM (10.3 g/dL, 73.0 ng/ml, 19.8%, respectively) and Venofer (10.3 g/dL, 75.1 ng/mL, and 19.6%, respectively). Baseline GFR-MDRD was 32.5 in FCM and 32.3 in Venofer. The proportion of subjects with a baseline hemoglobin ≤9.0 g/dL was 8.1% in FCM and 7.9% in Venofer.

The majority of subjects in both groups were No EPO users (FCM: 82.0%; Venofer: 82.3%), or CKD stage 3-4 (FCM: 87.2%; Venofer: 86.0%). The majority of subjects in both groups had no

history of myocardial infarction (FCM: 84.6%; Venofer: 85.7%), no stroke (FCM: 87.1%; Venofer: 87.8%), or no congestive heart failure (FCM: 75.3%; Venofer: 76.0%). Approximately, 54% subjects received previous iron therapy (FCM: 54.5%; Venofer: 53.9%), and majority of subjects in both groups had no history of iron intolerance (FCM: 94.7%; Venofer: 95.1%). The majority of demographic and baseline characteristics for the safety population were approximately balanced between the two treatment groups.

Statistical Methodologies

The change from baseline to the highest hemoglobin any time between baseline and the end of treatment period (Day 56) (or time of intervention) was assessed by comparing the 95% 2-sided CI (based on normal distribution, assuming equal variances) to a noninferiority margin of 0.2 g/dL.

For the proportion of subjects achieving an increase in hemoglobin of ≥1 g/dL any time between baseline and the end of treatment period (Day 56) (or time of intervention), the proportion difference between the treatment groups was estimated with a 95% 2-sided CI based on the normal approximation for the binomial distribution, using the Wald continuity correction. Noninferiority was to be concluded if the lower limit of the 2-sided CI is ≥-0.075.

Results and Conclusions

The efficacy evaluation population was a modified intent-to-treat (mITT) population who received at least one dose of randomized study medication, had at least one post-baseline hemoglobin assessment, and had a stable (± 20%) erythropoiesis stimulating agent (ESA) for four weeks, which may include a dose of zero, before randomization. There were 2493 subjects (1249 FCM versus 1244 Venofer) in the mITT population.

Primary Efficacy Analysis:

Table 6 : Mean Change in Hemoglobin from Baseline to the Highest Value between Baseline and Day 56 (or time of intervention): mITT Population (Study 1VIT9030)

	FCM (N=1249)	Venofer (N=1244)
Baseline		
Mean (SD)	10.31 (0.83)	10.33 (0.83)
Highest		
Mean (SD)	11.44 (1.19)	11.25 (1.08)
Change		
Mean (SD)	1.13 (1.04)	0.92 (0.92)
Difference (95% CI)	0.21 (0.13, 0.28)	

The estimated mean difference between FCM and Venofer was 0.21 g/dL with 95% CI of (0.13, 0.28). FCM was noninferior to Venofer in mean change in hemoglobin with the lower limit (0.13) of the 95% CI above the noninferiority margin of -0.2 g/dL. FCM was even statistically

superior to Venofer on the mean change in hemoglobin from baseline to the highest value during the study period.

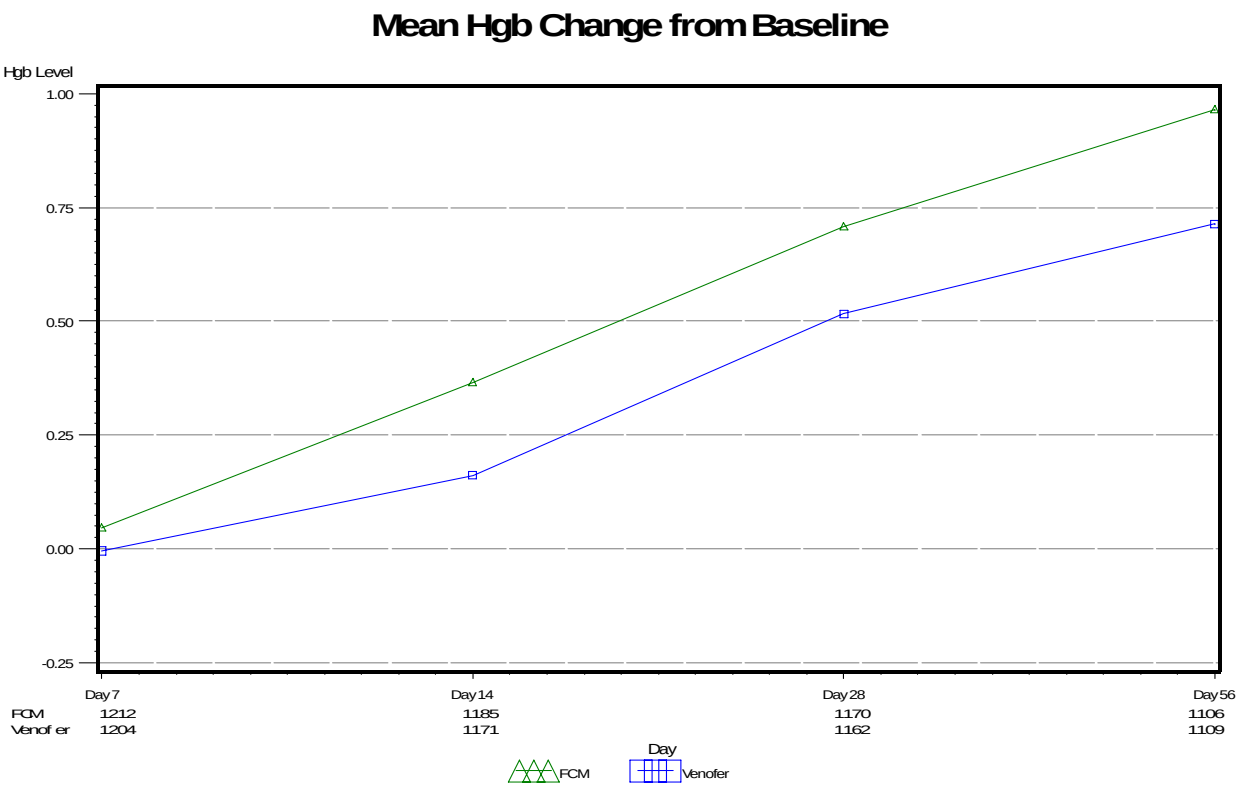
Reviewer's comment:
The maximum hemoglobin reached during the study period is summarized in table below.

	Early Termination n (%)	Day 7 n (%)	Day 14 n (%)	Day 28 n (%)	Day 56 n (%)	Retest n (%)
FCM (N=1249)	5 (0.4)	102 (8.2)	161 (12.9)	313 (25.1)	659 (52.8)	9 (0.7)
Venofer (N=1244)	7 (0.6)	139 (11.2)	136 (10.9)	360 (28.9)	590 (47.4)	12 (1.0)

The majority of subjects reached their maximum hemoglobin in the Day 56 (52.8% in FCM and 47.4% in Venofer).

Mean hemoglobin level change from Day 7 through Day 56 by groups is plotted in Figure 1.

Figure 1: Mean Hemoglobin Change from Baseline (Study 1VIT9030)



Supportive Efficacy Endpoints:
Results for supportive efficacy endpoints are summarized in Table 7.

Table 7 : Percent of Subjects With an Increase in Hemoglobin ≥ 1.0 g/dL Anytime Between Baseline and Day 56 (or time of intervention): mITT population (Study 1VIT9030)

	FCM (1249)	Venofer (N=1244)	
	n (%)	n (%)	95% CI
Hgb > 1.0 g/dL	607 (48.6)	510 (41.0)	7.6 % (3.6%, 11.5%)

The percent of subjects with an increase in hemoglobin ≥1.0 g/dL anytime between baseline and Day 56 (or time of intervention) demonstrated the noninferiority of FCM to Venofer because the treatment difference 95% CI lower limit of 3.6% was above a noninferiority margin of -7.5%. In addition, FCM was superior to Venofor with respect to the proportion of subjects with an increase in hemoglobin ≥1.0 g/dL with 95% CI of (3.6, 11.5) during the study period.

The supportive analyses of mean changes in hemoglobin, ferritin, TSAT, serum iron, total iron binding capacity (TIBC), unsaturated IBC from baseline to the highest values between baseline and Day 56 (or time of intervention) are summarized in Table 8.

Table 8 : Mean Change in Ferritin, TSAT, Serum Iron, TIBC, Unsaturated IBC from Baseline to the Highest Value between Baseline and Day 56 ((or time of intervention)): mITT Population (Study 1VIT9030)

	FCM (N=1249)	Venofer (N=1244)
Ferritin		
Baseline		
Mean (SD)	72.7 (64.2)	75.2 (64.3)
Highest		
Mean (SD)	807.4 (353.8)	364.1 (202.0)
Change		
Mean (SD)	734.7 (337.8)	288.9 (169.8)
Difference	445.8	
95% CI	(424.8, 466.9)	
TSAT		
N	1247	1243
Baseline		
Mean (SD)	19.75 (7.8)	19.60 (7.4)
Highest		
Mean (SD)	49.22 (18.9)	35.87 (15.3)
Change		
Mean (SD)	29.46 (17.0)	16.27 (14.2)
Difference	13.19	
95% CI	(12.0, 14.4)	

Serum Iron			
N	1248		1243
Baseline			
Mean (SD)	53.01 (20.2)		52.69 (20.1)
Highest			
Mean (SD)	124.21 (69.2)		95.91 (68.0)
Change			
Mean (SD)	71.19 (65.4)		43.22 (66.6)
Difference		27.97	
95% CI		(22.8, 33.2)	
Total Iron Binding Capacity (TIBC)			
N	1248		1243
Baseline			
Mean (SD)	277.75 (58.2)		277.29 (59.1)
Highest			
Mean (SD)	262.74 (59.7)		274.38 (62.1)
Change			
Mean (SD)	-15.01 (40.8)		-2.92 (39.8)
Difference		-12.09	
95% CI		(-15.3, -8.9)	
Unsaturated IBC			
N	1248		1243
Baseline			
Mean (SD)	224.74 (60.8)		224.45 (59.7)
Highest			
Mean (SD)	176.31 (52.5)		206.37 (52.1)
Change			
Mean (SD)	-48.43 (42.5)		-18.08 (30.0)
Difference		-30.34	
95% CI		(-33.2, -27.5)	

The mean increases in ferritin, TSAT, and serum iron and mean decreases in TIBC and unsaturated IBC from baseline to the highest values between baseline and Day 56 (or time of intervention) was statistically significantly greater subjects in FCM than subjects in Venofer.

3.2.2 1VIT9031

Study Design and Endpoints

Study 1VIT9031 was a Phase 3, multicenter, randomized, active-controlled study to compare the efficacy and safety of FCM in subjects who had IDA in the two cohorts. The two cohorts are as follows;
Cohort 1: Oral iron in subjects who had an unsatisfactory response to a 14-day oral iron run-in (defined as subject whose hemoglobin values increases <1 g/dL from baseline despite ≥67% compliance based on pill count), had TSAT and ferritin values that continued to meet the

inclusion criteria (including hemoglobin <12 g/dL) and no exclusion criteria were stratified by etiology of their IDA (HUB, GI disorders, and other), baseline hemoglobin (<9, 9.1 to 10.0, ≥10.1 g/dL), and baseline cardiovascular risk (Category 0-1 or 2-3 based on the Framingham Model) to receive either IV FCM or continuation of oral iron for another 14 days.

- Group A (FCM) received 15 mg/kg (postpartum subjects used pre-pregnancy weight) to a maximum of 750 mg per dose, administered on Days 0 and 7 (for a total maximum cumulative dose of 1,500 mg). It was administered as an undiluted IV push at100 mg/minute.
- Group B (oral) received ferrous sulfate 325 mg PO, TID for an additional 14 days

Cohort 2: IV standard of care (SC; other IV iron) in subjects who were shown to be intolerant of oral iron during the run-in or were felt to be inappropriate for an oral run-in. Subjects with documented adverse events of severe diarrhea, vomiting, constipation, or abdominal pain due to the oral iron during the Run-In Phase, subjects who experienced other symptoms due to the oral iron during the Run-In Phase had their dose of ferrous sulfate reduced to 325 mg PO once per day. If they had a ≥1 g/dL increase in hemoglobin, they were not randomized. If they did not have ≥1 g/dL increase in their hemoglobin on Day 15 of the Run-In Phase (despite ≥67% compliance with the reduced dose schedule) or if subjects continued to experience symptoms due to the oral iron despite the reduced dose, subjects whose physicians felt a subject was inappropriate for a 15-day course of oral iron but who otherwise satisfied the entry criteria were randomized 1:1 ratio to Groups C or D at the completion of the 14-day Run-In Phase.

- Group C (FCM) received 15 mg/kg (postpartum subjects used pre-pregnancy weight) to a maximum of 750 mg per dose, administered on Days 0 and 7 (for a total maximum cumulative dose of 1,500 mg). It was administered as an undiluted IV push at 100 mg/minute.
- Group D (IV standard care (SC)) received IV SC (other IV iron) as determined by the study site physician.

All subjects were required to return on Day -7 to assess compliance and tolerance of the oral iron. Randomized subjects returned for efficacy and safety evaluations which included adverse events and laboratory assessments on Days 7, 14, and 35. In addition, subjects were contacted on Day 90 and returned to the clinic on Day 120 to be assessed for adverse events.

The primary efficacy endpoint was the mean change from baseline to the highest observed hemoglobin observed anytime between baseline and Day 35 (or time of intervention) only in Cohort 1.

In Cohort 1, supportive efficacy measures included:

- Proportion of subjects achieving a hemoglobin value >12 g/dL anytime between baseline and Day 35 (or time of intervention).
- Mean change from baseline to the highest observed ferritin observed anytime between baseline and Day 35 (or time of intervention).
- Proportion of subjects achieving a hemoglobin value >12 g/dL and an increase in ferritin ≥160 ng/mL anytime between baseline and Day 35 (or time of intervention). The 2 criteria did not need to be met on the same day.
- Proportion of subjects achieving a clinically meaningful increase in hemoglobin anytime between baseline and Day 35 (or time of intervention). Clinically meaningful increase

was defined as ≥1 g/dL for CKD, ≥2 g/dL for HUB or GI disorders, ≥3 g/dL for postpartum, and ≥2 g/dL for others.
- Mean change from baseline to each scheduled visit for hemoglobin, TSAT, and ferritin.

In Cohort 2, supportive efficacy measures included:
- Mean change from baseline to the highest observed hemoglobin observed anytime between baseline and Day 35 (or time of intervention).
- Proportion of subjects achieving a hemoglobin value >12 g/dL anytime between baseline and Day 35 (or time of intervention).
- Mean change from baseline to the highest observed ferritin observed anytime between baseline and Day 35 (or time of intervention).
- Proportion of subjects achieving a hemoglobin value ≥12 g/dL and an increase in ferritin ≥160 ng/mL anytime between baseline and Day 35 (or time of intervention). The 2 criteria did not need to be met on the same day.
- Proportion of subjects achieving a clinically meaningful increase in hemoglobin anytime between baseline and Day 35 (or time of intervention). Clinically meaningful increase was defined as ≥1 g/dL for CKD, ≥2 g/dL for HUB or GI disorders, ≥3 g/dL for postpartum, and ≥2 g/dL for others.
- Mean change from baseline to each scheduled visit for hemoglobin, TSAT, and ferritin

The primary safety measure was the proportion of subjects experiencing at least one treatment-emergent adverse event included in the primary composite safety endpoint. Treatment-emergent events include events that start on or after the first dose of randomized treatment. The composite safety endpoints which were adjudicated by the CES committee of (b) (4) include:
- Death due to any cause
- Nonfatal myocardial infarction
- Nonfatal stroke
- Unstable angina requiring hospitalization
- Congestive heart failure requiring hospitalization or medical intervention
- Arrhythmias
- Hypertension
- Hypotension

Patient Disposition, Demographic and Baseline Characteristics

Sample size determination:
The planned sample size of 250 subjects per group was calculated based on the mean increase difference from baseline to the highest observed hemoglobin observed anytime between baseline and Day 35 of 0.47 g/dL, with a standard deviation of 1.6 g/dL. This sample size provided >90% power to detect a treatment group difference for the assessment of superiority of Group A versus Group B with respect to the mean increase from baseline to the highest hemoglobin on Day 35.

The difference between FCM and oral iron in mean change from baseline to the highest hemoglobin was 0.7 g/dL, with standard deviation 1.59 g/dL in 1VIT4002/4003. In VIT-IV-CL-008, the treatment differences were 0.8 and 0.5 g/dL at Weeks 4 and 8, respectively. No change

to maximum hemoglobin over 35 days was calculated in VIT-IV-CL-008, but the average of these 2 treatment differences was 0.65 g/dL.

A total of 1497 subjects received oral iron during the Run-in phase, of which 1011 subjects were randomized from 84 centers in the US to Cohort 1 (250 subjects in Group A and 257 subjects in Group B) or Cohort 2 (253 subjects in Group C and 251 subjects in Group D).

Among 1011 subjects, 4 subjects from Group A, 4 subjects from Group B, and 6 subjects from Group D discontinued from the study prior to dosing. A total of 246 subjects in the group A, 253 subjects in the Group B and Group C and 245 subjects in the Group D were treated.
The patient disposition is summarized in Table 9 for the treated population.

Table 9: Patient Disposition (Study 1VIT9031): Treated Population

Subjects Treated	Cohort 1 Group A (N=246)	Group B (N=253)	Cohort 2 Group C (N=253)	Group D (N=245)	Total (N=997)
Completed Treatment Phase (Screening-Day 35)	196 (79.7%)	206 (81.4%)	210 (83.0%)	195 (79.6%)	807 (80.9%)
Not completed Treatment Phase (Screening-Day 35)	50 (20.3%)	47 (18.6%)	43 (17.0%)	50 (20.4%)	190 (19.1%)
Adverse Event	4 (1.6%)	1 (0.4%)	2 (0.8%)	4 (1.6%)	11 (1.1%)
Selection criteria/compliance	32 (13.0%)	33 (13.0%)	31 (12.3%)	33 (13.5%)	129 (12.9%)
Lost to follow-up	9 (3.7%)	10 (4.0%)	7 (2.8%)	10 (4.1%)	36 (3.6%)
Subject request	5 (2.0%)	3 (1.2%)	2 (0.8%)	2 (0.8%)	12 (1.2%)
Other	0	0	1 (0.4%)	1 (0.4%)	2 (0.2%)
Completed Study Period (Screening-Day 120)	200 (81.3%)	204 (80.6%)	192 (75.9%)	187 (76.3%)	783 (78.5%)
Not completed Study Period (Screening-Day 120)	46 (18.7%)	49 (19.4%)	61 (24.1%)	58 (23.7%)	214 (21.5%)
Adverse Event	2 (0.8%)	3 (1.2%)	4 (1.6%)	4 (1.6%)	13 (1.3%)
Selection criteria/compliance	26 (10.6%)	24 (9.5%)	35 (13.8%)	35 (14.3%)	120 (12.0%)
Lost to follow-up	12 (4.9%)	18 (7.1%)	14 (5.5%)	15 (6.1%)	59 (5.9%)
Subject request	4 (1.6%)	4 (1.6%)	3 (1.2%)	1 (0.4%)	12 (1.2%)
Physician decision	1 (0.4%)	0	0	0	1 (0.1%)
Other	1 (0.4%)	0	5 (2.0%)	3 (1.2%)	9 (0.9%)

The percent of subjects completing the Treatment phase (Screening-Day 35) were 79.7%, 81.4%, 83%, and 79.6%, in Group A, B, C, and D, respectively. The most common reason that a subject did not complete the Treatment Phase was selection criteria/compliance (32, 33, 31 and 33 subjects in Group A, B, C, and D, respectively).

The percent of subjects completing the Study Period (Screening-Day 120) were 81.3%, 80.6%, 75.9%, and 76.3%, in Group A, B, C, and D, respectively. The most common reason that a subject did not complete the Treatment Phase was selection criteria/compliance (26, 24, 35 and 35 subjects in Group A, B, C, and D, respectively).

The total number of subjects who completed the study period was greater than the total number of subjects who completed the treatment period because of two different completion criteria. A subject completed the treatment phase had to have received both doses of FCM and completed the Day 35 Visit on Days 35-40. A subject completed the study period needed to have only one dose of study drug and a safety follow-up on Days 120-125.

The patient demographic characteristics are summarized in Table 10 for the treated population.

Table 10: Demographic Characteristics (Study 1VIT9031): Treated Population

	Cohort 1		Cohort 2	
	Group A: FCM (N=246) n (%)	Group B: Oral Iron (N=253) n (%)	Group C : FCM (N=253) n (%)	Group D: IV SC (N=245) n (%)
Age				
Mean (SD)	43.1 (17.2)	43.5 (17.7)	43.6 (16.9)	42.6 (15.5)
≤65	214 (87.0)	218 (86.2)	220 (87.0)	222 (90.6)
66-75	16 (6.5)	17 (6.7)	19 (7.5)	12 (4.9)
≥76	16 (6.5)	18 (7.1)	14 (5.5)	11 (4.5)
Gender				
Female	233 (94.7)	238 (94.1)	239 (94.5)	231 (94.3)
Male	13 (5.3)	15 (5.9)	14 (5.5)	14 (5.7)
Race				
African American	95 (38.6)	98 (38.7)	63 (24.9)	62 (25.3)
Asian	2 (0.8)	1 90.4)	0	3 (1.2)
Caucasian	67 (27.2)	79 (31.2)	135 (53.4)	136 (55.5)
Hispanic	79 (32.1)	69 (27.3)	51 (20.2)	41 (16.7)
Other	3 (1.2)	6 (2.4)	4 (1.6)	3 (1.2)
Weight, n				
Mean (SD)	246	253	252	245
BMI (kg/m²), n	82.8 (22.4)	84.2 (24.8)	79.5 (20.4)	84.7 (25.9)
Mean (SD)	246	253	252	245
	31.2 (8.4)	31.6 (8.5)	29.7 (7.6)	31.3 (8.9)

In Cohort 1, mean age was 43.1 years in FCM and 43.5 years in Oral Iron, respectively. Subjects age > 65 years (FCM: 87.0%; Oral Iron: 86.2%) and female subjects (FCM: 94.7%; Oral Iron 94.1%) were the majority. In FCM, 38.6 % of the subjects were African American and 27.2% were Caucasian. In Oral Iron, 38.7% subjects were African American and 31.2% subjects were Caucasian.

In Cohort 2, mean age was 43.6 years in FCM and 42.6 years in IV SC. Subjects age >65 years (FCM:87.0%; IV SC 90.6%) and female subjects (FCM: 94.5%; IV SC: 94.3%) were the majority.

The baseline characteristics for the treated population are summarized in Table 11.

Table 11: Baseline Characteristics (Study 1VIT9031): Treated Population

	Cohort 1		Cohort 2	
	Group A: FCM (N=246) n (%)	Group B: Oral Iron (N=253) n (%)	Group C: FCM (N=253) n (%)	Group D: IV SC (N=245) n (%)
Baseline Hgb				
Mean (SD)	10.6 (1.0)	10.6 (1.1)	9.1 (1.6)	9.0 (1.5)
≤9.0 g/dL	23 (9.3)	24 (9.5)	122 (48.2)	120 (49.0)
9.1-10.g/dL	48 (19.5)	48 (19.0)	60 (23.7)	60 (24.5)
≥10.1 g/dL	175 (71.1)	181 (71.5)	71 (28.1)	65 (26.5)
Baseline TSAT				
Mean (SD)	22.1 (14.8)	22.4 (15.1)	11.5 (12.2)	10.3 (9.7)
Baseline Ferritin				
Mean (SD)	31.3 (67.7)	28.2 (39.2)	25.9 (63.8)	14.9 (29.3)
EPO Use				
No	246 (100)	253 (100)	248 (98.0)	240 (98.0)
Yes	0	0	5 (2.0)	5 (2.0)
Etiology of IDA				
HUB	126 (51.2)	124 (49.0)	111 (43.9)	109 (44.5)
GI disorders	26 (10.6)	27 (10.7)	59 (23.3)	56 (22.9)
Other	94 (38.2)	102 (40.3)	83 (32.8)	80 (32.7)
Cardiac risk factors				
Any cardiac risk factor	100 (40.7)	107 (42.3)	103 (40.7)	104 (42.4)
Age >75	16 (6.5)	19 (7.5)	14 (5.5)	12 (4.9)
Prior cardiac disease	13 (5.3)	17 (6.7)	24 (9.5)	18 (7.3)
Current smoker	14 (5.7)	17 (6.7)	25 (9.9)	21 (8.6)
Hypertension/medication	72 (29.3)	77 (30.4)	65 (25.7)	70 (28.6)
Hyperlipidemia/use of lipid-lowering agent	35 (14.2)	43 (17.0)	36 (14.2)	38 (15.5)
Diabetes	34 (13.8)	48 (19.0)	25 (9.9)	28 (11.4)
Cardiovascular risk Category				
0-1	191 (77.6)	185 (73.1)	200 (79.1)	188 (76.7)
2-3	55 (22.4)	68 (26.9)	53 (20.9)	57 (23.3)
History of Iron Intolerance				
No	241 (98.0)	248 (98.0)	183 (72.3)	175 (71.4)
Yes	5 (2.0)	5 (2.0)	70 (27.7)	70 (28.6)
Prior Iron Therapy				
No	117 (47.6)	113 (44.7)	67 (26.5)	62 (25.3)
Yes	129 (52.4)	140 (55.3)	186 (73.5)	183 (74.7)

In Cohort 1, mean hemoglobin, ferritin, and TSAT values at baseline were well balanced between FCM (10.6 g/dL, 31.3 ng/ml, 22.1%, respectively) and Oral Iron (10.6 g/dL, 28.2 ng/mL, and 22.4%, respectively). The proportion of subjects with a baseline hemoglobin ≤ 9.0 g/dL was 9.3% in FCM and 9.5% in Oral Iron.

No subject used EPO and the majority of subjects had HUB in the etiology of IDA (FCM: 51.2%; Oral Ion: 49.0%). Approximately, over 40% of the subjects had any cardiac risk factors

(FCM: 40.7%; Oral Iron: 42.3%). Among cardiac risk factors, hypertension or on hypertensive medication were the most common factors (FCM: 29.3%; Oral Iron: 30.4%) and majority of subjects had cardiovascular risk of 0-1 (FCM: 77.6%; Oral Iron: 73.1%). The majority of subjects in both groups had no history of Iron Intolerance (98%). Approximately, over half of subjects received previous iron therapy (FCM: 52.4%; Oral Iron: 55.3%). The demographic and baseline characteristics for the safety population were approximately balanced between the two treatment groups in Cohort 1.

In Cohort 2, mean hemoglobin and TSAT values at baseline were well balanced between FCM (9.1 g/dL, 11.5%, respectively) and IV SC (9.0g/dL and 10.3%, respectively). The proportion of subjects with a baseline hemoglobin ≤9.0 g/dL was 48.2% in FCM and 49.0% in IV SC. The baseline mean ferritin value was higher in FCM than in IV SC (FCM: 25.9 ng/ml IV SC: 14.9 ng/ml).

The majority of subjects did not use EPO in both groups (98%) and had HUB in the etiology of IDA (FCM: 43.9%; IV SC: 44.5%). Approximately, over 40% of the subjects had any cardiac risk factors (FCM: 40.7%; IV SC: 42.4%). Among cardiac risk factors, hypertension or on hypertensive medication were the common factors (FCM: 25.7%; IV SC: 28.6%) and majority of subjects had cardiovascular risk of 0-1 (FCM: 79.1%; IV SC: 76.7%). The majority of subjects in both groups had no history of Iron Intolerance (FCM: 72.3%; IV SC: 71.4%) and received previous iron therapy (FCM: 73.5%; IV SC: 74.7%). The demographic and baseline characteristics for the safety population were approximately balanced between the two treatment groups in Cohort 2 except the baseline mean ferritin.

Statistical Methodologies

The mean change from baseline to the highest hemoglobin any time between baseline and Day 35 (or time of intervention) was analyzed using the analysis of covariance (ANCOVA) with treatment and etiology of IDA as fixed factors and baseline hemoglobin as a covariate.

Similarly, the mean changes of supportive efficacy endpoints were analyzed using the ANCOVA. The comparison between two groups on dichotomous response was analyzed using the Cochran-Mantel-Haenzel (CMH) test by adjusting for stratification factors.

All efficacy analyses were performed with the mITT Population, which included all treated subjects who received at least 1 dose of randomized study medication and had at least one post-baseline hemoglobin assessment.

Results and Conclusions

Table 12: Mean Change in Hemoglobin from Baseline to the Highest Value between Baseline and Day 35 (or time of intervention) (mITT) (Cohort 1 in Study 1VIT9031)

	FCM (N=244)	Oral Iron (N=251)
N	244	251
Baseline		
Mean (SD)	10.59 (1.01)	10.62 (1.03)
Highest		
Mean (SD)	12.16 (1.11)	11.42 (1.18)
Change		
Adjusted Mean*	1.52	0.76
Adjusted Difference (95% CI)*	0.76 (0.59, 0.93)	
p-value *	<0.0001	

*:ANCOVA with treatment and etiology of IDA as fixed factors and baseline hemoglobin as a covariate.

The estimated difference in the mean change in hemoglobin from baseline to the highest value between baseline and Day 35 (or time of intervention) between FCM and oral iron was 0.76 g/dL with 95% CI of (0.59, 0.93) (P<0.0001). FCM was statistically superior to oral iron in the mean change in hemoglobin from baseline to the highest value between baseline and Day 35 (or time of intervention) after adjusting for etiology.

Supportive Efficacy

The hemoglobin mean change from baseline to the highest value during study period is summarized in Table 13.

Table 13: Mean Change in Hemoglobin from Baseline to the Highest Value between Baseline and Day 35 (or time of intervention) (mITT) (Cohort 2 in Study 1VIT9031)

	FCM (N=245)	IV SC (N=237)
Baseline		
Mean (SD)	9.12 (1.60)	9.02 (1.47)
Highest		
Mean (SD)	12.02 (1.22)	11.17 (1.26)
Change		
Adjusted Mean*	2.93	2.12
Adjusted Difference (95% CI)*	0.81 (0.61, 1.00)	
p-value *	<0.0001	

*:ANCOVA with treatment and etiology of IDA as fixed factors and baseline hemoglobin as a covariate.

The estimated mean difference between FCM and IV SC was 0.81 g/dL with 95% CI of (0.61, 1.00) (P<0.0001). FCM was statistically superior to IV SC in mean hemoglobin change from baseline to the highest value between baseline and Day 35 (or time of intervention) after adjusting for etiology.

The proportion of subjects who achieved a hemoglobin >12.0g/dL any time from baseline to the study period is summarized in Table 14.

Table 14: Proportion of Subjects Achieving a Hemoglobin >12.0 g/dL Anytime between Baseline and Day 35 (or time of intervention): mITT population (Study 1VIT9031)

	Cohort 1		Cohort 2	
	FCM (N=244) n (%)	Oral Iron (N=251) n (%)	FCM (N=245) n (%)	IV SC (N=237) n (%)
Hgb >12 g/dL	139 (57.0)	73 (29.1)	124 (50.6)	58 (24.5)
p-value	<0.0001		<0.0001	
Baseline Hgb				
≤ 9 g/dL	9/23 (39.1)	2/23 (8.7)	49/117 (41.9)	12/116 (10.3)
9.1-10 g/dL	21/48 (43.8)	5/48 (10.4)	31/58 (10.4)	16/58 (27.6)
≥ 10.1 g/dL	109/173 (63.0)	66/180 (36.7)	44/70 (36.7)	30/63 (47.6)
Etiology of IDA				
HUB	79/125 (63.2)	36/123 (29.3)	64/108 (59.3)	24/106 (22.6)
GI disorders	12/56 (46.2)	4/27 (14.8)	12/57 (50.9)	13/53 (24.5)
Other	48/93 (51.6)	33/101 (32.7)	31/80 (38.8)	21/78 (26.9)

The proportion of subjects with a hemoglobin value >12.0 g/dL anytime between baseline and Day 35 (or time of intervention) was statistically significantly greater in the FCM group than that of the comparator group (oral iron in Cohort 1 and IV SC in Cohort 2) (P<0.0001). A greater proportion of subjects in the FCM group had a hgb>12g/dL anytime between baseline and Day 35 (or time of intervention) than the comparator group in the hgb and etiology of IDA categories.

The ferritin mean change from baseline to the highest value during the study period is summarized in Table 15.

Table 15: Mean Change in Ferritin from Baseline to the Highest Value between Baseline and Day 35 (or time of intervention): mITT Population (Cohort 1 in Study 1VIT9031)

	Cohort 1		Cohort 2	
	FCM (N=244)	Oral Iron (N=251)	FCM (N=245)	IV SC (N=237)
Baseline				
Mean (SD)	30.86 (67.4)	28.16 (39.2)	25.17 (63.3)	14.26 (28.2)
Highest				
Mean (SD)	569.29 (317.0)	34.55 (50.0)	543.20 (405.2)	145.08 (192.8)
Change				
Adjusted Mean*	532.34	3.55	518.03	130.82
Adjusted Difference (95% CI)*	528.8 (496.4, 561.1)		369.8 (317.6, 422.1)	
p-value *	< 0.0001		<0.0001	

*:ANCOVA with treatment and etiology of IDA as fixed factors and baseline hemoglobin as a covariate.

The mean increase in ferritin from baseline to the highest value between baseline and Day 35 (or time of intervention) was statistically significantly greater in the FCM group than that of the comparator group (oral iron in Cohort 1 and IV SC in Cohort 2).

The proportion of subjects who had hemoglobin >12.0g/dL increase and ferritin ≥ 160 ng/mL increase during the study period is summarized in Table 16.

Table 16: Proportion of Subjects with Hemoglobin >12.0 g/dL and an Increase in Ferritin ≥ 160 ng/mL Anytime between Baseline and Day 35 (or time of intervention): mITT population (Study 1VIT9031)

	Cohort 1		Cohort 2	
	FCM (N=244) n (%)	Oral Iron (N=251) n (%)	FCM (N=245) n (%)	IV SC (N=237) n (%)
Hgb >12 g/dL and Ferritin ≥ 160ng/mL				
	133 (54.5)	1 (0.4)	118 (48.2)	14 (5.9)
P-value	<0.0001		<0.0001	
Baseline Hgb				
≤ 9 g/dL	8/23 (34.8)	0/23	46/117 (39.3)	4/116 (3.4)
9.1-10 g/dL	19/48 (39.6)	0/48	29/58 (50.0)	4/58 (6.9)
≥ 10.1 g/dL	106/173 (61.3)	1/180 (0.6)	43/70 (61.4)	6/63 (9.5)
Etiology of IDA				
HUB	76/125 (60.8)	1/123 (0.8)	61/108 (56.5)	6/106 (5.7)
GI disorders	12/56 (46.2)	0/27	27/57 (47.4)	4/53 (7.5)
Other	45/93 (48.4)	0/101	30/80 (37.5)	4/78 (5.1)

The proportion of subjects with a hemoglobin value >12.0 g/dL and an increase in ferritin ≥160 ng/mL anytime between baseline and Day 35 (or time of intervention) was statistically significantly greater in the FCM group than that observed in the comparator group (oral iron in Cohort 1 and IV SC in Cohort 2). The results were consistent to the all baseline hemoglobin (≤9.0 g/dL, 9.1-10.0 g/dL, and ≥10.1 g/dL) categories and etiology of IDA (HUB, GI disorders, and other).

The clinically meaningful increase was defined as ≥1 g/dL for CKD, ≥2 g/dL for HUB or GI disorders, ≥3 g/dL for postpartum, and ≥2 g/dL for others. The proportion of subjects with a clinically increase in hemoglobin is summarized in Table 17.

Table 17: Proportion of Subjects with a Clinically Meaningful Increase in Hemoglobin Anytime between Baseline and Day 35 (or time of intervention): mITT Population (Study 1VIT9031)

	Cohort 1		Cohort 2	
	FCM (N=244) n (%)	Oral Iron (N=251) n (%)	FCM (N=245) n (%)	IV SC (N=237) n (%)
Clinically Meaningful Increase in Hgb				
	80 (32.8)	22 (8.8)	164 (66.9)	113 (47.7)
P-value	<0.0001		<0.0001	
Baseline Hgb				
≤ 9 g/dL	19/23 (82.6)	1/23 (4.3)	107/117 (91.5)	74/116 (63.8)
9.1-10 g/dL	20/48 (41.7)	6/48 (12.5)	36/58 (62.1)	25/58 (43.1)
≥ 10.1 g/dL	41/173 (23.7)	15/180 (8.3)	21/70 (30.0)	14/63 (22.2)
Etiology of IDA				
HUB	43/125 (34.4)	12/123 (9.8)	78/108 (72.2)	48/106 (45.3)
GI disorders	12/56 (46.2)	1/27 (3.7)	37/57 (64.9)	22/53 (41.5)
Other	25/93 (26.9)	9/101 (8.9)	49/80 (61.3)	43/78 (55.1)

The proportion of subjects who had a clinically meaningful increase in hemoglobin anytime between baseline and Day 35 (or time of intervention) was statistically significantly greater in the FCM group compared to the comparator group (oral iron in Cohort 1 and IV SC in Cohort 2). The results were consistent to the all baseline hemoglobin (≤9.0 g/dL, 9.1-10.0 g/dL, and ≥10.1 g/dL) categories and etiology of IDA (HUB, GI disorders, and other).

The mean changes in hemoglobin, ferritin, TSAT, serum iron, TIBC, unsaturated IBC from baseline to the highest values between baseline and Day 35 (or time of intervention) are summarized in Tables 18 and 19.

Table 18: Mean Change in Hemoglobin and Other Iron Indices from Baseline to Day 35 (or time of intervention): mITT Population (Cohort 1 in Study 1VIT9031)

	FCM			Oral Iron		
	N	Baseline Mean (SD)	Change to Day 35 (SE)	N	Baseline Mean (SD)	Change to Day 35 (SE)
Hemoglobin (g/dL)	199	10.62 (1.0)	1.58 (1.2)	204	10.70 (1.0)	0.58 (0.8)
Adjusted Mean (SE)			1.54 (0.08)			0.57 (0.08)
Ferritin (ng/mL)	200	32.89 (73.0)	264 2 (224.2)	207	27.45 (34.4)	-3.83 (26.7)
Adjusted Mean (SE)			256.11 (10.0)			-3.19 (10.1)
TSAT (%)	199	21.42 (13.8)	12.99 (16.3)	204	32.34 (15.7)	-5.70 (15.9)
Adjusted Mean (SE)			12.31 (1.0)			-5.04 (1.0)
Serum Iron (µg/dL)	199	72.44 (56.6)	10.49 (57.2)	204	76.82 (57.6)	-22.05 (57.8)
Adjusted Mean (SE)			8.65 (2.8)			-20.31 (2.8)
TIBC (µg/dL)	199	327.12 (60.7)	-81.40 (46.5)	204	325.13 (55.0)	-0.66 (39.8)
Adjusted Mean (SE)			-81.17 (3.0)			-1.26 (3.0)
Unsaturated IBC (µg/dL)	199	254.69 (71.1)	-91.89 (63.2)	203	248.87 (73.0)	19.16 (62.7)
Adjusted Mean (SE)			-90.79 (4.0)			17.08 (4.1)

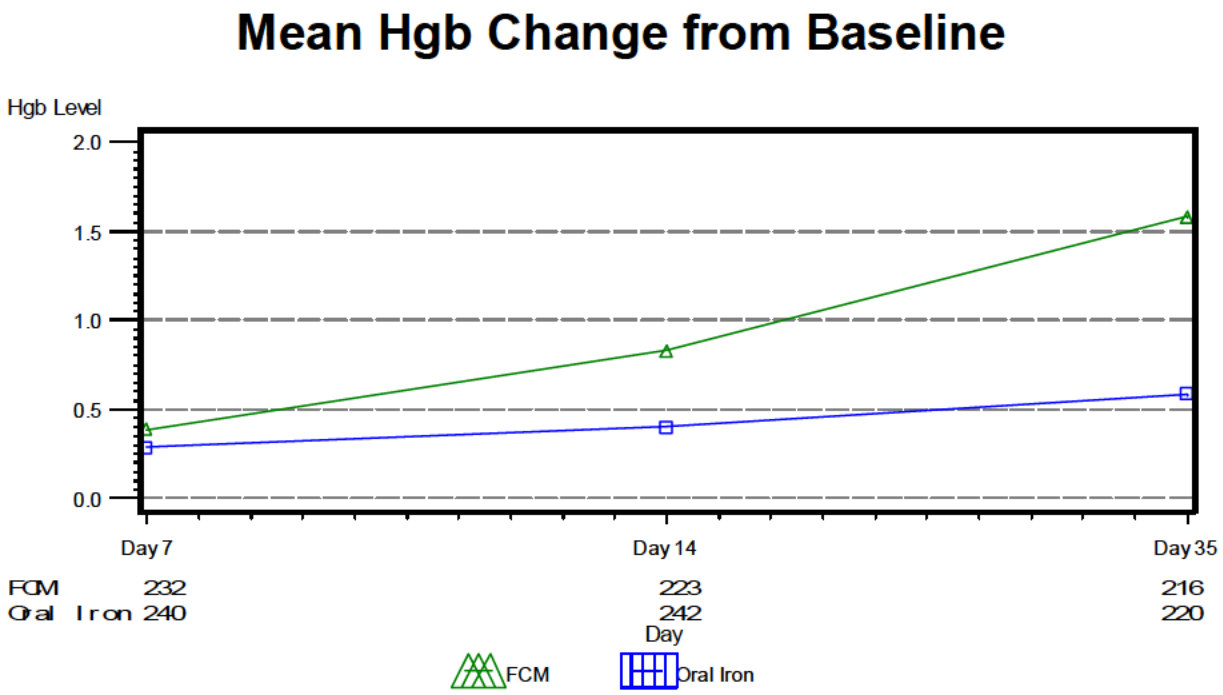
The mean increases in ferritin, TSAT, and serum iron and mean decreases in TIBC and unsaturated IBC from baseline to each scheduled visit between baseline and Day 35 (or time of intervention) were statistically significantly greater in FCM than in oral iron.

Table 19: Mean Change in Hemoglobin and Other Iron Indices from Baseline to Day 35 (or time of intervention): mITT Population (Cohort 2 in Study 1VIT9031)

	FCM			Oral Iron		
	N	Baseline Mean (SD)	Change to Day 35 (SE)	N	Baseline Mean (SD)	Change to Day 35 (SE)
Hemoglobin (g/dL)	220	9.12 (1.6)	2.87 (1.7)	202	9.03 (1.5)	2.13 (1.3)
Adjusted Mean (SE)			2.91 (0.08)			2.10 (0.08)
Ferritin (ng/mL)	223	26.56 (66.0)	218.15 (211.4)	204	14.45 (29.7)	74.65 (115.7)
Adjusted Mean (SE)			212.64 (10.3)			88.23 (10.7)
TSAT (%)	221	11.69 (12.6)	20.18 (15.5)	205	10.30 (9.8)	8.77 (12.7)
Adjusted Mean (SE)			20.73 (0.8)			8.31 (0.8)
Serum Iron (µg/dL)	221	42.34 (63.2)	35.51 (66.5)	205	35.97 (34.3)	19.54 (41.1)
Adjusted Mean (SE)			38.31 (2.0)			16.47 (2.1)
TIBC (µg/dL)	221	359.19 (80.8)	-108.62 (66.2)	205	368.61 (67.7)	-60.92 (51.8)
Adjusted Mean (SE)			-112.12 (2.7)			-58.53 (2.7)
Unsaturated IBC(µg/dL)	221	316.85 (91.8)	-144.13 (82.4)	205	332.65 (78.9)	-80.48 (68.3)
Adjusted Mean (SE)			-150.17 (3.5)			-75.92 (3.6)

The mean increases in ferritin, TSAT, and serum iron and mean decreases in TIBC and unsaturated IBC from baseline to each scheduled visit (including Day 7) between baseline and Day 35 (or time of intervention) were statistically significantly greater in FCM than in IV SC.

Figure 2: Mean Hemoglobin Change from Baseline (Study 1VIT9031)



3.3 Evaluation of Safety

The primary composite safety endpoint was the time to the first event of following events.

- Deaths due to any cause.
- Nonfatal myocardial infarction (MI).
- Nonfatal stroke.
- Unstable angina requiring hospitalization.
- Congestive heart failure requiring hospitalization or medical intervention.
- Arrhythmias.
- Protocol-defined hypertensive events.
- Protocol-defined hyposensitive events.

This primary composite safety endpoint for study 1VIT9030 is summarized in Table 20.

Table 20: Primary Composite Safety Endpoint: Safety Population (Study 1VIT9030)

	FCM (N=1276)	Venofer (N=1285)	Difference (95% CI)
Any Events	175 (13.7%)	156 (12.1%)	1.6 (-1.1, 4.3)
Death	15 (1.2%)	18 (1.4%)	-0.2 (-1.2,-0.7)
Nonfatal MI	8 (0.6%)	14 (1.1%)	-0.5 (-1.3,0.3)
Nonfatal stroke	3 (0.2%)	3 (0.2%)	0.0 (-0.5, 0.5)
Unstable angina	11 (0.9%)	3 (0.3%)	0.6 (-0.02, 1.3)
Heart failure	38 (3.0%)	34 (2.7%)	0.3 (-1.0, 1.7)
Arrhythmias	18 (1.4%)	13 (1.0%)	0.4 (-0.5, 1.3)
Hypertensive	95 (7.5%)	56 (4.4%)	3.1 (1.2, 5.0)
Hypotensive	23 (1.8%)	41 (3.2%)	-1.4 (-2.7, -0.1)

A total of 175 subjects (13.7%) in FCM and 156 subjects (12.1%) in Venofer experienced the primary composite safety endpoint events, which was independently adjudicated by the (b) (4) CEC committee. The 95% confidence interval for the treatment difference was -1.1% to 4.3%.

The most common component of the primary composite safety endpoint was protocol-defined hypertensive events in both the FCM (7.5%) and Venofer (4.4%) groups with a 95% confidence interval for the difference between the treatment groups of (1.2, 5.0).

The primary composite safety endpoint analyses were performed for overall events, excluding hypertensive or hypotensive events, and only for deaths, MI or stroke events. The results were summarized in Table 21.

Table 21: Summary Results for Primary Composite Safety Endpoint Analyses (Study 1VIT9030)

	FCM (N=1312)	Venofer (N=1311)
Any Events	175 (16.7%)	156 (12.1%)
Diff. (95% CI)	1.6 (-1.1, 4.3)	
Excluding hyper & hypotensive	70 (5.5%)	69 (5.4%)
Diff. (95% CI)	0.12 (-1.7, 2.0)	
Death, MI, or Stroke	24 (1.9%)	35 (2.7%)
Diff. (95% CI)	-0.84 (-2.1, 0.4)	

After excluding protocol-defined hypertensive or hypotensive events, 5.5% of subjects in FCM and 5.4% of subjects in Venofer were experienced primary composite safety events (95% CI for the difference: -1.7%, 2.0%). The composite of death, myocardial infarction (MI), or stroke occurred 1.9% of subjects in FCM vs. 2.7% of subjects in Venofer.

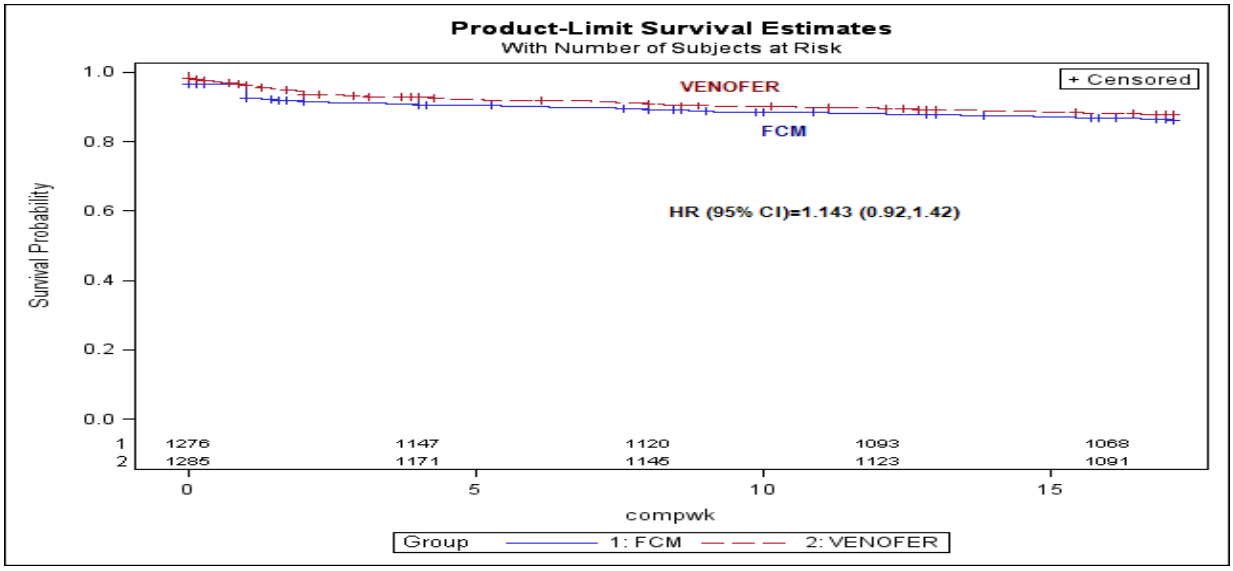
The time to first event of primary composite safety endpoint analyses were performed for overall events, excluding hypertensive or hypotensive events, and only for deaths, MI or stroke events using Cox proportional hazard regression models. The results were summarized in Table 22.

Table 22: Cox Proportional Hazard Analyses Results for Primary Composite Safety Endpoint (Study 1VIT9030)

	FCM (N=1312)	Venofer (N=1311)
Any Events	175 (16.7%)	156 (12.1%)
HR (95% CI)	1.14 (0.92, 1.42)	
Excluding hyper & hypotensive	70 (5.5%)	69 (5.4%)
HR (95% CI)	1.02 (0.73, 1.42)	
Death, MI, or Stroke	24 (1.9%)	35 (2.7%)
HR (95%CI)	0.69 (0.41, 1.15)	

The hazard ratio for the time to first event comprising the primary composite safety endpoint was 1.143 (CI=0.92, 1.42). The hazard ratio was 1.017 (CI=0.73, 1.42) after excluding protocol-defined hypertensive and hypotensive events. The hazard ratio was 0.685 (CI=0.41, 1.15) for the major cardiac events of death, myocardial infarction, and stroke.

Figure 3: Kaplan Meier Curves for the Primary Composite Safety Endpoint (Study 1VIT9030)



This primary composite safety endpoint for study 1VIT9031 is summarized in Table 23.

Table 23: Primary Composite Safety Endpoint: Safety Population (Study 1VIT9031)

	Cohort 1		Cohort 2	
	Group A FCM (N=246)	Group B Oral Iron (N=253)	Group C FCM (N=253)	Group D IV SC (N=245)
Any Events	7 (2.9%)	4 (1.6%)	10 (4.0%)	17 (3.4%)
Death	0	2 (0.8%)	1 (0.4%)	1 (0.4%)
Nonfatal MI	0	0	1 (0.4%)	0
Nonfatal stroke	0	1 (1.4%)	0	0
Unstable angina	0	1 (1.4%)	0	0
Heart failure	0	0	0	0
Arrhythmias	0	1(1.4%)	0	0
Hypertensive	4 (1.6%)	0	7 (2.8%)	6 (2.5%)
Hypotensive	3 (1.2%)	1 (1.4%)	1 (0.4%)	5 (2.0%)

A total of 7 subjects (2.9%) in FCM (Group A), and 4 subjects (1.6%) in Oral Iron (Group B) experienced the primary composite safety endpoint events in Cohort 1. A total of 10 subjects (4.0%) in FCM (Group C), and 12 subjects (4.9%) in Oral Iron (Group B) experienced the primary composite safety endpoint events in Cohort 2.

The most common component of the primary composite safety endpoint was protocol-defined hypertensive events in FCM (1.6%), death due to any cause in Oral Iron (0.8%), protocol-defined hypertensive events in FCM (2.8%), and protocol-defined hypertensive events in IV SC (6. 5%).

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The study was designed to address a question about the differences in effects in the entire population, not to address questions about subgroups. These subgroup analyses should be considered with caution.

4.1 Gender, Race, Age, and Geographic Region

Subgroup analyses for gender, race and age groups (<65 years versus ≤ 65 years) of the primary endpoints (Study 1VIT9030 and Cohort 1 for Study 1VIT9031) are summarized in Table 25 and Table 26 below for both studies. More female than male and more >65 years than ≤ 65 years old subjects were observed for both studies. More Caucasian than other race was observed in Study 1VIT9030, but more African American than other race was observed in Study 1VIT9031 (Cohort 1).

The 95% 2-sided confidence interval (CI) based on normal distribution were calculated for Study 1VIT9030 and least square estimates and 95% CI were calculated using ANCOVA models with

treatment and etiology of IDA as fixed factors and baseline hemoglobin as a covariate for Cohort 1 in the Study 1VIT9031.

Table 24: Study 1VIT9030 Subgroup Analyses for Mean Change in Hemoglobin from Baseline to the Highest Value between Baseline and Day 56 (or time of intervention): Age, Gender and Race: mITT Population

	n	Baseline Mean	Highest Mean	Mean Change (SD)	Difference (95% CI)
Age <65					
FCM	461	10.28	11.52	1.24 (0.98)	
Venofer	489	10.24	11.17	0.93 (0.93)	0.31 (0.18, 0.43)
Age ≥65					
FCM	788	10.32	11.39	1.07 (1.08)	
Venofer	755	10.38	11.29	0.92 (0.91)	0.15 (0.05, 0.25)
Female					
FCM	794	10.33	11.45	1.12 (1.02)	
Venofer	794	10.33	11.28	0.95 (0.93)	0.17 (0.07, 0.27)
Male					
FCM	455	10.28	11.42	1.15 (1.08)	
Venofer	450	10.32	11.20	0.87 (0.90)	0.27 (0.14, 0.40)
African American					
FCM	329	10.23	11.24	1.02 (0.96)	
Venofer	311	10.25	11.06	0.81 (0.86)	0.21 (0.06, 0.35)
Asian					
FCM	20	10.40	11.27	0.87 (0.72)	
Venofer	20	10.09	10.83	0.74 (1.09)	0.14 (-0.46, 0.73)
Caucasian					
FCM	664	10.40	11.60	1.21 (1.13)	
Venofer	670	10.39	11.40	1.01 (0.95)	0.20 (0.09, 0.31)
Hispanic					
FCM	224	10.18	11.30	1.12 (0.91)	
Venofer	233	10.27	11.11	0.84 (0.87)	0.29 (0.13, 0.45)
Other					
FCM	12	9.87	10.33	0.46 (0.73)	
Venofer	10	10.05	11.03	0.98 (1.01)	-0.52 (-1.30, 0.25)

The primary endpoint results were fairly consistent across subgroups. Except for the "Other" race group, all point estimates favor the FCM arm. The 95% CI for the difference between FCM and Venofer in mean change from baseline to the highest observed hemoglobin any time between baseline and end of treatment period (Day 56) (or time of intervention) were higher than -0.20 g/dL (noninferiority margin) except for the "Other" race.

Table 25: Study 1VIT9031 Subgroup Analyses for Mean Change in Hemoglobin from Baseline to the Highest Value between Baseline and Day 35 (or time of intervention): Age, Gender and Race: mITT Population

	n	Baseline Mean	Highest Mean	Mean Change (SD)	Difference* (95% CI)
Age <65					
FCM	210	10.67	12.27	1.60 (1.22)	
Oral Iron	214	10.68	11.51	0.82 (0.80)	0.77 (0.59, 0.95)
Age ≥65					
FCM	34	10.12	11.49	1.37 (1.01)	
Oral Iron	37	10.28	10.91	0.63 (0.77)	0.71 (0.28, 1.15)
Female					
FCM	232	10.60	12.18	1.57 (1.19)	
Oral Iron	237	10.64	11.44	0.79 (0.80)	0.76 (0.59, 0.93)
Male					
FCM	12	10.48	11.97	1.49 (1.32)	
Oral Iron	14	10.24	11.12	0.88 (0.86)	0.62 (-0.32, 1.56)
African American					
FCM	95	10.75	11.86	1.11 (0.95)	
Oral Iron	98	10.67	11.27	0.60 (0.66)	0.55 (0.34, 0.75)
Asian					
FCM	2	10.13	12.70	2.58 (0.32)	
Oral Iron	1	9.30	12.20	2.90 (.)	
Caucasian					
FCM	66	10.37	12.18	1.81 (1.20)	
Oral Iron	78	10.51	11.34	0.83 (0.92)	0.92 (0.57, 1.26)
Hispanic					
FCM	78	10.60	12.50	1.90 (1.30)	
Oral Iron	68	10.68	11.63	0.95 (0.76)	0.91 (0.59, 1.23)
Other					
FCM	3	10.87	12.57	1.70 (1.39)	
Oral Iron	6	10.91	12.28	1.38 (0.64)	0.12 (-1.26, 1.51)

* Least square mean difference and 95% CI from ANCOVA with treatment and etiology of IDA as fixed factors and baseline hemoglobin as a covariate.

The direction of the estimated treatment differences for subgroup analyses results were consistent. See table.

4.2 Other Special/Subgroup Populations

The primary endpoint is the mean change from baseline to the highest value during the study period.

The mean change in hemoglobin from baseline to the highest value during the study period is summarized by baseline hemoglobin categories in Table 26.

Table 26 : Mean Change in Hemoglobin from Baseline to the Highest Value between Baseline and Day 56 ((or time of intervention)) by Baseline Hemoglobin: mITT Population (Study 1VIT9030)

Baseline Hgb	FCM (N=1299)	Venofer (N=1244)
≤9.0 g/dL		
N	100	96
Baseline		
Mean (SD)	8.43 (0.52)	8.48 (0.56)
Highest		
Mean (SD)	10.13 (1.68)	9.92 (1.25)
Difference	0.26	
95% CI	(-0.15, 0.68)	
9.1-10.0 g/dL		
N	280	279
Baseline		
Mean (SD)	9.60 (0.29)	9.60 (0.31)
Highest		
Mean (SD)	10.89 (1.13)	10.74 (1.05)
Difference	0.15	
95% CI	(-0.02, 0.33)	
≥10.1 g/dL		
N	869	869
Baseline		
Mean (SD)	10.75 (0.41)	10.76 (0.42)
Highest		
Mean (SD)	11.76 (0.95)	11.56 (0.87)
Difference	0.22	
95% CI	(0.14, 0.30)	

Subjects with baseline hemoglobin ≥10.1 g/dL had statistically significantly greater mean changes in hemoglobin in FCM than in Venofer. Subjects with baseline hemoglobin ≤9.0 g/dL and 9.1-10.0 g/dL had no difference in the mean changes between the two groups. FCM was noninferior to Venofer because the lower bounds of 95% CI were above the noninferiority margin of -0.20g/dL.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The key statistical issues and findings are as follows:

- For Study 1VIT9030, the estimated mean difference between FCM and Venofer was 0.21 g/dL with 95% CI of (0.13, 0.28). FCM was noninferior to Venofer in mean change in hemoglobin with the lower limit (0.13) of the 95% CI above the noninferiority margin of -0.2 g/dL. FCM was even statistically superior to Venofer on the mean change in hemoglobin from baseline to the highest value during the study period.

- The primary composite safety endpoint of the Study 1VIT9030 was the proportion of death, nonfatal myocardial infarction, nonfatal stroke, unstable angina requiring hospitalization, congestive heart failure, arrhythmias, protocol-defined hypertensive and hypotensive events. A total of 175 subjects (13.7%) in FCM and 156 subjects (12.2%) in Venofer had one or more events with 95 % CI of (-1.1, 4.3). The most common event among the primary composite safety endpoint was protocol-defined hypertensive events, 7.5% in FCM and 4.4% in Venofer, respectively. After excluding protocol-defined hypertensive and hypotensive events, 5.5% subjects in FCM and 5.4% subjects in Venofer had events. Subjects with death, nonfatal myocardial infarction or nonfatal stroke were observed 1.9% in FCM and 2.7% in Venofer.

- The proportion of subjects with an increase in hemoglobin $\geq$ 1.0 g/dL from baseline to the end of study period not only demonstrated noninferiority with lower bound of 3.6 % (> noninferiority margin of -7.5%) but also superiority with 95% CI (3.6, 11.5) of FCM to Venofer in study 1VIT9030.

- For Study 1VIT9030, the mean increases in ferritin, TSAT, and serum iron and mean decreases in TIBC and unsaturated IBC from baseline to the highest value from baseline to the end of study period were statistically significantly greater for subjects in the FCM arm compared to subjects in the Venofer arm.

- For study 1VIT9031, subjects in FCM demonstrated superiority to Oral Iron in Cohort 1 which included oral iron subjects who had an unsatisfactory response to a 14-day oral iron run-in with an estimated difference between FCM and oral iron of 0.76 g/dL and 95% CI of (0.59, 0.93) (P<0.0001) with respect to the mean change in hemoglobin from baseline to the highest value between baseline and Day 35 (or time of intervention) after adjusting for etiology.

- For study 1VIT9031, all supportive efficacy endpoints for Cohort 1 and Cohort 2 were superior for subjects in the FCM arm compared to subjects in the oral Iron arm in Cohort 1. Similar finding applied to the IV SC arm in Cohort 2.

5.2 Conclusions and Recommendations

The observed mean changes in hemoglobin from baseline to the highest values during the study period demonstrated clinical benefit in subjects who had iron deficiency anemia impaired renal function with non-dialysis dependent chronic kidney disease (CKD) (1VIT9030) and oral iron subjects who had an unsatisfactory response to a 14-day oral iron run-in (1VIT9031).

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Kyung Yul Lee, Ph.D.
Date:

Concurring Reviewer(s):

Statistical Team Leader: Dr. Rothmann

Biometrics Division Deputy Director: Dr. Gwise

cc:
Project Manager: Ms. Baird
Medical Officer: Dr. Min
Medical Team Leader: Dr. Robie Suh
Primary Statistical Reviewer: Dr. Lee
Statistical Team Leader: Dr. Rothmann
Biometrics Division Deputy Director: Dr. Gwise
Lillian Patrician

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KYUNG Y LEE
06/28/2012

MARK D ROTHMANN
06/28/2012

THOMAS E GWISE
06/28/2012

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 203565 **Applicant:** **Stamp Date: 10/3/2011**

Sanofi Aventis

Drug Name: Ferinject **NDA/BLA Type: NDA**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ____yes____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	
Appropriate references for novel statistical methodology (if present) are included.			x	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	x			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

File name: 5_Statistics Filing Checklist for a NDA203565

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Kyung Yul Lee, Ph.D.

Reviewing Statistician Date

Mark Rothmann, Ph.D.

Supervisor/Team Leader Date

File name: 5_Statistics Filing Checklist for a NDA203565

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12/14/2011