FDA Advisory Committee Briefing Document

Drug Safety and Risk Management Committee
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Consultative assistance from the Office of Clinical Pharmacology and the Office of Biostatistics

New Drug Application (NDA) 22-054 for Injectafer (Ferric Carboxymaltose) for the treatment of iron deficiency anemia in patients with heavy uterine bleeding or postpartum patients

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Publication: Amanzadeh, J, Reilly, R. Hypophosphatemia: an evidence-based approach to its clinical consequences and management. Nature Clinical Practice Nephrology 2: 136-147; 2006.	64

Topics for Questions for Advisory Committee Members:

1. The committee will be asked to discuss the importance of the mortality data in the Injectafer clinical development program.

2. Based upon considerations of the overall risks and benefits of Injectafer, FDA plans to request advice regarding marketing approval of the drug for the proposed indication.

3. FDA anticipates the marketing approval discussion to involve considerations of:
- the need for additional clinical studies (either prior to approval or as a post-marketing commitment),
- a risk management plan,
- modification of the proposed indication or dosage regimen to enhance safety.

Executive Summary

1. Product Background:

Injectafer (Ferric Carboxymaltose, from Luitpold Pharmaceuticals, Inc.) is the subject of a New Drug Application (NDA) for the indication of, "treatment of iron deficiency anemia in: heavy uterine bleeding (*or*) postpartum patients."

The proposed market population includes patients who might otherwise receive oral iron as a treatment option. Consequently, the bulk of the clinical data assessing Injectafer safety and efficacy were obtained from studies that compared Injectafer to oral iron. Injectafer is not specifically proposed for use as an alternative to other parenteral iron products or for patients who are intolerant of oral iron.

The Injectafer dosage regimen allows potentially a full iron replenishment dosage with three or fewer intravenous administrations, contingent upon the body's estimated iron deficit and certain limits upon a single dosage. Specifically, the dose is determined by calculating the total iron requirement and dividing this total amount into one or more single dose(s). The proposed dose regimen allows for the rapid intravenous (IV) push injection (single dose ≤ 500 mg) or IV infusion of up to a maximum dose of 1,000 mg (or 15 mg/kg) for the first dose. The maximum single doses may be administered every seven days until the total iron requirement has been administered or a maximum of 2,500 mg has been administered. Consequently, a "cycle" may be viewed as consisting of the weekly dosage regimens that delivered the full iron replacement dose or a maximum of 2,500 mg iron.

2. Clinical and Drug Class Background

Iron deficiency anemia, one of the most common forms of anemia, is generally due to the loss of body iron during hemorrhage or insufficient iron intake. In addition to treatment of the underlying cause of iron deficiency anemia (such as correction of bleeding), iron replenishment helps normalize blood hemoglobin levels and potentially lessen the duration or severity of anemia symptoms.

Many clinical situations are associated with the development of iron deficiency anemia, such as chronic hemodialysis, gastrointestinal hemorrhage due to various lesions, pregnancy and the postpartum condition, inflammatory bowel disease as well as hemorrhage due to uterine bleeding. The pathophysiology of the anemia in many of these considerations involves the interaction of multiple factors, such as hemorrhage, nutrition and malabsorption. The Injectafer clinical development program examined the use of the product in patients with iron deficiency anemia associated with chronic kidney disease (including patients undergoing hemodialysis), inflammatory bowel disease, heavy uterine bleeding as well as post-partum iron deficiency.

Iron replenishment may be necessary only for a short period of time; for example, following a single hemorrhage episode. Alternately, iron replenishment may be necessary over a long period of time due to on-going iron losses, as may occur with low-grade, recurrent hemorrhage. The Injectafer clinical development program for the

proposed indication generally focused upon the short term replacement of iron (through a maximum of a 2,500 mg iron deficit). Clinical data supporting the safety and efficacy of repeat Injectafer "cycles" were supplied from studies of patients with chronic kidney disease, a market population not currently cited in the proposed Injectafer indication.

While oral iron is probably the most common iron replacement product for the broad population of patients with iron deficiency, three iron products are currently marketed for intravenous use among some patients with iron deficiency anemia. These products consist of:

a. Iron dextran (for example, Dexferrum®, InFed®), indicated for patients with iron deficiency anemia (any cause) "in whom oral administration [of iron] is unsatisfactory or impossible."

b. Ferric gluconate (Ferrlecit®), indicated for patients with iron deficiency anemia who are undergoing chronic hemodialysis and receiving erythropoietin therapy.

c. Iron sucrose (Venofer®), indicated for patients with iron deficiency anemia who are:
- non-dialysis dependent chronic kidney disease patients (receiving an erythropoietin or not)
- hemodialysis dependent chronic kidney disease patients receiving an erythropoietin
- peritoneal dialysis dependent chronic kidney disease patients receiving an erythropoietin.

3. Dosage Considerations:

The maximum iron dose for administration at any one time (single dose) for most currently marketed parenteral iron products is generally 200 mg or less. However, Venofer is approved for use as a maximum of a 400 mg single dose administration to certain patients undergoing peritoneal dialysis. The maximum Venofer (single) dose is limited to 200 mg in other patient populations.

If approved, Injectafer would be relatively unique among the parenteral iron products in that the maximum (single) Injectafer dose is 1,000 mg (or 15 mg/kg).

4. Efficacy Data:

The major efficacy outcomes in the Injectafer clinical development program related to detection of change in blood hemoglobin concentrations. In general, the studies enrolled patients with iron deficiency anemia and used changes in hemoglobin concentrations as the primary efficacy endpoints. The endpoints compared either the proportions of patients achieving a pre-specified definition of anemia correction or a comparison of the change in hemoglobin value between baseline and a pre-specified time point.

The studies were not designed sufficiently to meaningfully assess potential clinical benefits beyond changes in hemoglobin concentration. For example, most studies were

open label such that unbiased assessment of any changes in "health-related quality of life" in these studies is impossible due to knowledge of the treatment assignment.

The efficacy studies consistently showed that Injectafer administration increased blood hemoglobin concentrations. Hence, the supplied data provide substantial evidence of the efficacy of Injectafer in iron replenishment.

5. Safety

The major safety concern from the clinical development program relates to a mortality safety signal as evidenced by three notable findings, as listed below.

a. An imbalance in death rates:

In the entire clinical development program, death occurred among 10 patients who received Injectafer while one death occurred among a patient who received a control drug (Venofer). Five of the 10 deaths among patients receiving Injectafer appeared to relate to a cardiac abnormality.

Studies in the development program varied in design, including the use of a 1:1 randomization for several controlled studies, a randomized cross-over design (placebo-Injectafer) for one major study, an uneven randomization ratio in some controlled studies as well as uncontrolled studies. Nevertheless, the deaths among patients receiving Injectafer were distributed among multiple studies.

Within the pool of randomized, controlled studies (that included a placebo-controlled, randomized, cross-over study), six deaths occurred among patients in the Injectafer group and one death in a patient treated with Venofer. Exclusive of the randomized, cross-over study, deaths in randomized, controlled studies consisted of 5/1206 (0.4%) for Injectafer and 1/994 (0.1%) for the control iron product.

b. An imbalance in reports of serious adverse events, especially serious cardiac events:

Within the pool of active-controlled, multicenter studies, a serious adverse event was reported by 43/1206 (3.6%) of Injectafer-treated patients and 21/834 (2.5%) of patients receiving oral iron (control product). Serious "cardiac" events were reported in 13/1206 (1.1%) of Injectafer-treated patients and 3/834 (0.4%) of patients receiving oral iron (control product).

c. An imbalance in the occurrence of "clinically important" hypophosphatemia

Serum phosphorus was not measured rigorously in all clinical studies. However, data are available for the proposed market population. Specifically, 8% of postpartum patients and 70% of heavy uterine bleeding patients experienced "clinically important hypophasphatemia" following Injectafer administration. "Clinically important" hypophaphatemia was not reported among patients receiving oral iron. "Clinically

important" hypophasphatemia was defined as a serum phosphate concentration < 2 mg/dL.

Hence, the mortality safety signal is not based upon statistical comparisons. Instead, the clinical pattern of a numeric imbalance in mortality, combined with imbalances in serious adverse events (especially cardiac events) and clinically important hypophosphatemia suggest that the proposed Injectafer dose regimen may be associated with important safety concerns.

6. Purpose of the Advisory Committee Discussion

The Advisory Committee is convened to provide an independent assessment of the importance, if any, of the mortality safety signal detected in the Injectafer clinical development program. FDA anticipates asking the Committee to address topics related to the market approval of the product as well as considerations of additional clinical studies, potential dose modifications and potential alterations of the proposed indication.

The Committee discussion is a component of the regulatory review of the Injectafer NDA. The NDA was originally submitted to FDA in June, 2006 with a proposed indication related to use of the product among four groups of iron deficient patients:
-heavy uterine bleeding
-postpartum
-inflammatory bowel disease
-hemodialysis patients.

The original FDA review of the application culminated in issuance of a non-approvable letter related predominantly to the mortality safety signal. In response to the FDA letter, in September, 2007, the sponsor submitted a statistical assessment of the mortality data, study reports for two additional studies performed among patients with chronic kidney disease and responses to FDA questions. The proposed indication was also changed (in November, 2007) to indicate Injectafer only for patients with iron deficiency anemia in the post-partum condition or patients with heavy uterine bleeding.

In general, the sponsor does not concur with the FDA concern regarding a mortality safety signal and the proposed product label does not address the mortality finding. The Advisory Committee is convened to independently assess the clinical data and specifically, the data pertinent to assessment of a mortality safety signal.

Medical Summary Document

This summary consists of the most pertinent components of the medical officer's draft review document

December 28, 2007

In this document, Injectafer is sometimes referred to by other names used during the clinical development program (Ferinject, FCM or Vit-45).

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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
b.w.	Body weight
CAD	Coronary artery disease
CHF	Congestive heart failure
CKD	Chronic Kidney Disease
CI	Confidence Interval
CRF	Case report form
CRP	C-reactive protein
C-section	Cesarean Section
CTCAE	Common Toxicity Criteria for Adverse Event
dL	Deciliter
ECG/EKG	Electrocardiogram
EPO	Erythropoietin
ESRD	End Stage Renal Disease
FCM	Ferric carboxymaltose
Fe[III]	Ferric Iron
FeS04	Ferrous Sulfate
G	Gram
GFR	Glomerular filtration rate
GI	Gastrointestinal
GGT	Gamma-glutamyl transpeptidase
Hb	Hemoglobin
HD	Hemodialysis
Hct	Hematocrit
HUB	Heavy uterine bleeding
IBD	Inflammatory Bowel Disease
ICM	Iron Carboxymaltose
IDA	Iron Deficiency Anemia
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-To-Treat
IV	Intravenous
L	Liter
LFT	Liver function test
Mg	Milligram
MI	Myocardial infarction
MITT	Modified Intent to Treat
mL	Milliliter
NaCl	Sodium chloride
NDA	New Drug Application
ng	Nanogram
NSS	Normal Saline Solution
NYHA	New York Heart Association
PP	Per Protocol
r-HuEPO	Recombinant human erythropoietin
RBC	Red blood cell
SAE	Serious adverse event
SD	Standard Deviation
TIBC	Total iron binding capacity
TID	Three times daily
TSAT	Transferrin saturation
VIT-45	Ferinject/Injectafer
WBC	White Blood Cell

1. EXECUTIVE SUMMARY

Injectafer (Ferinject) is a Type I polynuclear iron (III)-hydroxide carbohydrate complex being developed as an intravenous iron product for treatment of iron deficiency anemia. The currently proposed indication is the treatment for iron deficiency anemia in patients with heavy uterine bleeding or post-partum patients with iron deficiency anemia. The proposed dose regimen is 1,000 mg as a single maximum dose weekly until administration of the total calculated iron requirement or a maximum total cumulative dose of 2,500 mg is reached.

Multiple clinical studies were performed during the Injectafer development program although four randomized controlled studies are especially pertinent to support the proposed indication for the treatment of iron deficiency anemia in women with heavy uterine bleeding (one study) or post-partum anemia (three studies). Of these four studies, efficacy results from two studies showed superiority of Injectafer to oral iron and two studies showed non-inferiority to oral iron. The supplied data indicates that Injectafer administration results in iron replenishment with improvement in blood hemoglobin concentrations.

The integrated review of safety included the results from 14 completed clinical studies. A total of 2080 patients in completed clinical studies were exposed to Injectafer treatment. In these studies, 1571 patients received the control treatments, including 834 who received oral iron product, 145 who received Venofer (iron sucrose) and 592 who received placebo (in a cross-over study and a single dose safety study).

The safety review raised concerns for Injectafer due to evidence of a mortality signal. Of note, the clinical development program was not designed to thoroughly assess mortality due to the relatively small database sample size (given the overall low mortality rate) and the study design features. For example, more subjects were exposed to Injectafer than a control drug since randomization was not consistently one to one. Nevertheless, the overall imbalance and pattern of mortality raises concerns.

The evidence of a mortality safety signal is based upon the numeric imbalance in deaths from a database insufficiently sized to rule out an important mortality risk for Injectafer as well as imbalances in serious adverse event rates (especially for cardiac events) and the excessive rate of hypophosphatemia among subjects receiving Injectafer.

The clinical database for Injectafer is open to multiple interpretations as to which studies should be classified among the "randomized, controlled studies" as well as to how the data should be analyzed based upon comparisons to oral iron or Venofer. Hence, in presentations, the sponsor and FDA may occasionally refer to data presentations that differ based upon differences in data pooling, data interpretation and the approach to summarization of the data.

Mortality

There were 10 deaths in Injectafer-treated patients as compared to one death in the control patients in all completed clinical studies. The 10 deaths in Injectafer-treated patients consisted of: one postpartum woman, one patient with inflammatory bowel disease, three patients undergoing chronic hemodialysis, four patients with non-dialysis dependent chronic renal failure, and one patient with multi-factorial iron deficiency anemia.

In randomized studies, six deaths were reported in Injectafer-treated patients and one death was reported in a control patient (a nominal rate of 0.33% vs. 0.06%). These randomized studies include a cross-over study (Study VIT05006) in which subjects were randomized between Injectafer and placebo, followed by the complimentary treatment one week later (one death occurred after "cross-over" to Injectafer in this study). Some analyses may eliminate this study from the group of "randomized, controlled" studies, given the cross-over nature of the study. In this situation, the data would be described as showing five deaths in the Injectafer group in "randomized, controlled" studies and one death in a control group.

Five of the six deaths among Injectafer-treated patients in randomized studies occurred in studies using the proposed first-dose 1,000 mg dose regimen. Four of these five patients received a single 1,000 mg dose and one patient received an initial 1,000 mg dose followed by lower subsequent doses.

Among the 10 Injectafer-treated patients who died, five had received a single dose of Injectafer (four received 1,000 mg and one received 200 mg) and five received two or more doses of Injectafer. The events leading to nine of 10 deaths occurred within 32 days of the last Injectafer administration. The sponsor had clinical information reviewed by external reviewers to determine the "cause" of death. Nevertheless, determination of the "cause" of a death is commonly difficult or impossible and all putative "causes" of death are suspect. The FDA review team nominally assessed the "causes" of deaths to include five cardiac disorders (two cardiac arrests, one anterior myocardial infarction, one heart failure and one cardiac insufficiency), three infections (two cases of sepsis, one bowel abscess and perforation), one gastrointestinal bleeding and one motor-vehicle accident.

Serious adverse events, especially "cardiac" events

Within the pool of active-controlled, multicenter studies, a serious adverse event was reported by 3.6% of Injectafer-treated patients and 2.5% of patients receiving oral iron (control product). Serious "cardiac" events were reported in 1.1% of Injectafer-treated patients and 0.4% of patients receiving oral iron (control product).

In general, the data pool especially pertinent to consideration of marketing approval consists of the group of controlled studies that examined the 1,000 mg (maximum) first dose Injectafer regimen. Within this data pool, the occurrence of serious adverse event as well as serious "cardiac" events was also unbalanced, with numerically more events among patients receiving Injectafer.

Hypophosphatemia

Serum phosphate decreased in Injectafer-treated patients as compared to oral iron-treated patients in the six clinical studies where serum phosphate levels were measured. The incidence of hypophosphatemia varied among the studies but the overall pattern indicates that Injectafer administration was associated with an increased risk of clinically significant hypophosphatemia, compared to control products. For example, 8% of postpartum and 70% of heavy uterine bleeding patients reached a nadir serum phosphate of < 2.0 mg/dL. The phosphate nadirs in the heavy uterine bleeding patients occurred at a median of 15 days and recovered at a median of 18 days.

2. BACKGROUND INFORMATION

2.1 Product Information

Injectafer (Ferinject) is a Type I polynuclear iron (III)-hydroxide carbohydrate complex being developed as an intravenous iron product for treatment of iron deficiency anemia.

Current available treatment for iron deficiency anemia includes oral iron products and intravenous iron products. Approved intravenous iron products include iron dextran, Ferrlecit (ferric gluconate) and Venofer (iron sucrose). With respect to the dose regimen for these other intravenous iron products, the generally recommended maximum single dose is 100 mg of elemental iron for iron dextran, 125 mg of elemental iron for Ferrlecit, and up to 400 mg for Venofer. Hence, the proposed maximum single dose of Injectafer (1,000 mg) is more than twice that of any currently approved intravenous iron product.

2.2 Proposed Indication

In the original NDA submission dated June 15, 2006, the proposed indication was the treatment of iron deficiency anemia in patients with heavy uterine bleeding, post-partum anemia, inflammatory bowel disease and hemodialysis. However, on November 14, 2007, the sponsor revised the proposed indication to the treatment of iron deficiency anemia in women with heavy uterine bleeding or post-partum patients with iron deficiency anemia. Despite the alteration of the proposed indication to a more narrow population of patients who may be healthier and less likely to need repeat "cycles" of Injectafer iron replenishment, FDA maintains that the totality of the clinical data from the development program are important to the assessment of Injectafer's risks and benefits.

2.3 Proposed Dose Regimen

Injectafer is administered intravenously either by rapid intravenous (IV) push injection or by IV infusion. The dose is determined by calculating the total iron requirement and dividing this total amount into one to three doses.

Total iron requirement (cumulative dose) in mgs: Patient weight in kg x (15 – current Hb g/dL) x 2.4 + 500. Maximum total dose not to exceed 2,500 mg.

- If patient is postpartum use pre-pregnancy weight
- If TSAT > 20% and ferritin > 50 ng/mL subtract 500 mg
- Round dose to nearest 100 mg

Maximum single dose must not exceed 15 mg/kg per dose or 1,000 mg, whichever is lower. The single doses should be administered every 7 days until the total iron requirement or a maximum of 2,500 mg is reached.

- 600 to 1,000 mg doses: Dilute in 250 mL of 0.9% Sodium Chloride, USP and administer by IV infusion over ≥ 15 minutes or undiluted IV push injection over 15 minutes
- ≤ 500 mg doses: Administer undiluted by IV push injection at 100 mg per minute

The sponsor's proposed label provides no specific recommendations regarding the Injectafer dosage for patients who may develop iron deficiency anemia following iron replenishment with a first "cycle" of Injectafer. Conceivably, additional "cycles" of Injectafer would be administered to these patients.

Repeat "cycle" data were supplied from studies conducted among patients with iron deficiency anemia who also had chronic kidney disease. Repeat "cycle" data have not been supplied for other patient populations, including women with heavy uterine bleeding and iron deficiency anemia or women with post-partum iron deficiency anemia.

3. CLINICAL STUDIES

3.1 Table of Clinical Studies

Fourteen clinical studies were completed to support the safety and efficacy of Injectafer for the indication for the treatment of iron deficiency anemia. The following table lists all completed clinical studies.

Summary of completed clinical studies

Study Populations	Studies	Type of studies	Injectafer group	Control group	Total patients enrolled
Heavy Uterine Bleeding	1VIT04002/ 1VIT04003	Randomized, open-label, parallel group, superiority study	246	231 (oral iron)	477
Post-partum Anemia	1VIT03001	Randomized, open-label, parallel group, non-inferiority study	182	179 (oral iron)	361
	VIT-IV-CL-009	Randomized, open-label, parallel group, non-inferiority study	231	118 (oral iron)	349
	1VIT06011	Randomized, open-label, parallel group, superiority study	143	148 (oral iron)	291
Inflammatory Bowel Disease	VIT-IV-CL-008	Randomized, open-label, parallel group, non-inferiority study	137	63 (oral iron)	200
	VIT-IV-CL-003	Single arm, baseline-controlled study	46	none	46

Hemodialysis	VIT-IV-CL-015	Randomized, open-label, parallel group study	119	119 (Venofer)	238
	VIT-53214	Single arm, baseline-controlled study	162	none	162
Non-dialysis Dependent chronic kidney disease	1VIT04004	Randomized, open-label, parallel group study	147	103	250
	1VIT05005 (extension of 1VIT04004)	Single arm, treatment extension safety study	127	none	127
Iron deficiency anemia (For safety only)	VIT-IV-CL-02	Single dose, PK and safety study	24	8 (Placebo)	32
	VIT-IV-CL-001	Single dose, PK and safety study	6	-	6
	1VIT05006	Single dose, cross-over safety study	584	569 (Placebo)	
Chronic heart failure	FER-CARS-01	Pilot, randomized, double-blind, controlled study	30	27 (Venofer) 15 (placebo)	72

3.2 Major Inclusion Criteria and Study Treatment

The following table shows the major inclusion criteria and study treatment in each study.

Major inclusion criteria and study treatment

Study populations	Studies	Major inclusion criteria	Study treatment and duration
Heavy Uterine Bleeding	1VIT04002/ 1VIT04003	Hb ≤11.4 g/dL and 2 mean Hb ≤11.0 g/dL TSAT ≤25%. Ferritin ≤100 ng/mL. History of heavy uterine bleeding within the past 6 months	**Injectafer:** Total (cumulative) dose= weight (kg) x (15- hemoglobin [g/dL]) x 2.4 + 500 mg If TSAT >20% and Ferritin >50 ng/mL subtract 500 mg Maximum single dose: 1000 mg Maximum cumulative dose: 2,500 mg Administration:
Post-partum Anemia	1VIT03001	Hb ≤10.0 g/dL TSAT ≤50%. Ferritin ≤500 ng/mL.	

		Within 10 days of delivery	200 mg: undiluted IV push over 1-2 minutes
	VIT-IV-CL-009	Hb ≤10.5 g/dL Within 6 days of delivery	300-400 mg: in 100 cc NS over 6 minutes 500-1,000 mg: in 250 cc NS over 15 minutes **Oral iron:** Ferrous sulfate 325 mg three times a day for 6 weeks for Studies 1VIT4002/04003 and 1VIT03001 Ferrous sulfate 100 mg twice daily for 12 weeks for Study VIT-IV-CL-009
	1VIT06011	Hb ≤10.0 g/dL TSAT ≤25%. Ferritin ≤100 ng/mL. Within 10 days of delivery	Same as Study 1VIT04002/04003 and 1VIT03001 except for administration: <500 mg: undiluted as a slow IV injection at a rate of 100 mg/minute 600-1000 mg: either undiluted as slow IV injection over 15 minutes or as an IV infusion diluted in 250 cc NSS over 15 minutes
Inflammatory Bowel Disease	VIT-IV-CL-008	Hb ≤11.0 g/dL TSAT <20%. Ferritin <100 ng/mL.	Injectafer: same as 1VIT04002/04003 Oral iron: Ferrous sulfate 100 mg twice daily for 12 weeks
	VIT-IV-CL-003	Iron deficiency anemia with a calculated total iron requirement ≥1000 mg	Injectafer: 500 mg/weekly x 4 doses or 1000 mg weekly x 2 doses Diluted in 250 cc NSS and infusion over 15 minutes
Hemodialysis	VIT-IV-CL-015	Hb ≤11.5 g/dL TSAT <20%. Ferritin <200 ng/mL.	Injectafer or Venofer: Total dose=weight (kg) x (15- hemoglobin [g/dL]) x 2.4 + 500 mg Administered 200 mg as undiluted directly into dialysis line two or three times weekly during hemodialysis
	VIT-53214	hemodialysis associated anemia	Injectafer: same as Study VIT-IV-CL-015
Non-dialysis dependent chro kidney disease	1VIT04004	Hb ≤11 g/dL TSAT <25%. Ferritin <300 ng/mL.	Day 0: 1000 mg Day 17 and 31: 500 mg if TSAT <30% and ferritin <500 ng/mL Administration: 201-500 mg: in 100 cc NS over 15 minutes 501-1,000 mg: in 250 cc NS over 15 minutes Oral iron: Ferrous sulfate 325 mg three times daily

			for 8 weeks
	1VIT05005 (extension of 1VIT04004)	Enrolled in 1VIT04004	1000 mg if TSAT<25% and ferritin <300 ng/mL 500 mg if TSAT<30% and ferritin <500 ng/mL
Iron deficiency anemia (for safety only)	1VIT05006	Hb ≤12 g/dL TSAT ≤25%. Ferritin <300 ng/mL for chronic kidney disease and inflammatory bowel disease. Ferritin <100 ng/mL for other anemia	Injectafer: 1000 mg single dose Placebo
Chronic heart failure	FER-CARS-01	Stable symptomatic CHF NYHA II-IV Hb 10-14.5 g/dL Ferritin <100 mg/L or Ferritin 100-300 mg/L with TSAT<20% or hypochromic red cells >10%	Injectafer or Venofer: 200 mg weekly until total calculated dose was reached.

4. EFFICACY FINDINGS

Four randomized controlled studies were conducted to support the currently proposed indication for the treatment of iron deficiency anemia in women with heavy uterine bleeding or post-partum anemia.

4.1 In women with heavy uterine bleeding

One study was a compilation of two studies (1VIT04002 and 1VIT04003) that were conducted and discontinued due to slow enrollment. The target enrollment was 390 patients in each study and at the time of discontinuation, 257 patients (66% of target) had enrolled in Study 1VIT04002 and 220 patients (56% of target) had enrolled in Study 1VIT04003. A pooled analysis with a separate analysis for each study was performed to support the efficacy.

Both studies were randomized, open-label, parallel group, oral-iron controlled superiority studies. The primary efficacy endpoint was an increase in hemoglobin ≥2.0 g/dL from baseline at anytime during the study. In the pooled analysis, 246 patients were randomized to the Injectafer group and 231 patients were randomized to the oral iron group. Treatment compliance in the oral iron group (defined as total iron received/expected) was 90%. There were significantly more patients who had a hemoglobin increase ≥2.0 g/dL from baseline during the study in the Injectafer group as compared to the oral iron group (82.0% vs. 61.8%, $p<0.01$) in the modified intent-to-treat population. Similar results were seen when analyzed for each study (82.5% vs. 63.5% in 1VIT04002 and 81.5% vs. 59.6% in 1VIT-4003; $P<0.001$ in both studies). The efficacy results are presented below.

Proportion of Subjects Who Achieved an Increase in Hemoglobin ≥2 g/dL from baseline at anytime during the Study

		Injectafer	Oral Iron	Fisher's exact p-value	95% CI
Combined analysis	Modified ITT Population	187/228 (82.0%)	139/225 (61.8%)	<0.001	12.2, 28.3
	Evaluable Population	177/213 (83.1%)	128/207 (61.8%)	<0.001	12.9, 29.6
Study 1VIT04002	Modified ITT Population	99/120 (82.5%)	80/126 (63.5%)	<0.001	8.2-29.8
	Evaluable Population	92/111 (82.9%)	74/116 (63.8%)	0.002	7.9-30.3
Study 1VIT04003	Modified ITT Population	88/108 (81.5%)	59/99 (59.6%)	<0.001	9.8-34.0
	Evaluable Population	85/102 (83.3%)	54/91 (59.3%)	<0.001	11.6-36.4

4.2 In women with post-partum anemia

Three studies (1VIT03001, VIT-IV-CL-009 and 1VIT06011) were submitted to support the indication in this population.

Study 1VIT03001

A total of 361 subjects were randomized in the study including 182 to the Injectafer group and 179 to oral iron group. Among these, 174 were treated in the Injectafer group and 178 were treated in the oral iron group. One hundred sixty-five (165; 91%) of 182 randomized subjects in the Injectafer group and 162 (91.0%) of 179 randomized subjects in the oral iron group completed the study. Treatment compliance in the oral iron group was 84%.

The primary efficacy endpoint was the proportion of subjects who achieved an increase in hemoglobin ≥2 g/dl from baseline at anytime during the study. There was no significant difference between the Injectafer and the oral iron groups in the proportion of patients who achieved an increase in hemoglobin ≥2.0 g/dL from baseline at anytime during the study (96.4% vs. 94.1%, P>0.05, 95% CI of difference: -2.2-6.9). The efficacy results are shown below.

Proportion of Subjects Who Achieved an Increase in Hemoglobin ≥2 g/dL from baseline at anytime during the Study

	Injectafer	Oral Iron	Fisher's exact p-value	95% CI (Inject-oral iron)
Modified ITT Population	162/168 (96.4%)	159/169 (94.1%)	0.443	-2.19, 6.88

Evaluable Population	158/162 (97.5%)	142/150 (94.7%)	0.243	-1.26, 6.99

The results were within the pre-specified non-inferiority margin of 15% on lower bound of 95% CI for treatment difference.

Study VIT-IV-CL-009

Among 349 randomized patients (231 to Injectafer and 118 to oral iron), 344 received at least one dose of study drug and had efficacy data available, and 268 (77%) patients were included in the evaluable population. Treatment compliance in the oral iron group was 90%.

The primary efficacy endpoint was the change in mean hemoglobin at Week 12. There was no significant difference between the Injectafer and the oral iron groups in the change in mean hemoglobin at Week 12 from baseline (3.37 g/dL vs. 3.29 g/dL, p>0.05, 95% CI of difference: -0.15-0.37). The efficacy results are shown below.

Change in mean hemoglobin at Week 12 from baseline

		Injectafer n Mean (SD)	Oral Iron n Mean (SD)	p-value	95% CI for treatment difference
Modified ITT Population	Hb at baseline	227 9.66 (1.46)	117 9.76 (1.58)		
	Hb at Week 12	216 12.96 (1.20)	109 12.87 (1.04)		
	Change in Hb	216 3.34 (1.79)	109 3.18 (1.76)	>0.05	-0.147-0.368
Evaluable Population	Hb at baseline	179 9.67 (1.47)	89 9.60 (1.28)		
	Hb at Week 12	179 13.04 (1.07)	89 12.89 (1.04)		
	Change in Hb	179 3.37 (1.77)	89 3.29 (1.69)	>0.05	-0.069-0.445

The results were within pre-specified non-inferiority margin of - 0.5 g/dL on lower bound of 95% CI for treatment difference for MITT and evaluable populations. In the study, there were 23% of patients who had major protocol violations or premature discontinuation of study treatment.

Study 1VIT06011

In Study 1VIT06011 , two hundred ninety-one (291) subjects (143 to Injectafer and 148 to oral iron) were randomized in the study. One subject in each arm discontinued the study prior to receiving a study drug dose due to subject's request. Overall, 138(97%) in

the Injectafer group and 144 (98.0%) in the oral iron group completed the study. Treatment compliance in the oral iron group was 96%.

The primary efficacy endpoint was hemoglobin >12 g/dL at anytime during the study between baseline and end of study (Day 42). There was a significantly higher proportion of patients who achieved hemoglobin >12 g/dl at anytime during the study in the Injectafer group as compared to oral iron group (88.8% vs. 66.2%, p<0.001). The efficacy results are shown below.

Proportion of Subjects Who Achieved a Hemoglobin ≥12 g/dL at anytime during the Study

	Injectafer	Oral Iron	Fisher's exact p-value	95% CI (VIT-45-oral iron)
Modified ITT Population	127/139 (91.4%)	98/147 (66.7%)	<0.001	15.20, 34.20
Evaluable Population	126/138 (91.3%)	96/143 (67.1%)	<0.001	14.65, 33.70
ITT population	127/143 (88.8%)	98/143 (66.2%)	<0.001	12.97, 32.22

Reviewer's table based on sponsor's data in amendment 28, Vol. 1

5. SAFETY FINDINGS

The integrated review of safety included the safety results from 14 completed clinical studies. A total of 2080 patients in completed clinical studies were exposed to Injectafer treatment. In these studies, a total of 1571 patients received the control treatments including 834 who received oral iron, 145 who received Venofer and 592 who received placebo (in a cross-over study and a single dose safety study).

The following table shows the number of exposed patients and dose regimen used in each study.

Summary of completed clinical studies for safety evaluation

Study populations	**Studies**	**Number of patients received Injectafer**	**Injectafer Dose regimen**	**Control group**
Iron deficiency anemia (CKD, IBD, Post-partum, HUB and other)	VIT-IV-CL-02	24	Single dose, 100, 500, 800, 1000 mg	Placebo (n=8)
	VIT-IV-CL-001	6	Single dose, 100 mg	None
	1VIT05006 Cross-over	584	Single dose, 15 mg/kg Maximum dose: 1,000 mg	Placebo (n=569)

	study			
Heavy Uterine Bleeding	1 VIT-4002/ 4003	230	Repeated doses until iron repletion using total iron requirement calculation. Maximum single dose: 1000 mg (15 mg/kg for weight of 66 kg) per week. Maximum cumulative dose: 2,500 mg	Oral iron (n=226)
Post-partum Anemia	1 VIT03001	174		Oral iron (n=178)
	VIT-IV-CL-009	227		Oral iron (n=117)
	1VIT06011	142		Oral iron (n=147)
Inflammatory Bowel Disease	VIT-IV-CL-008	137	Repeated doses until iron repletion using total iron requirement calculation. Maximum single dose: 1000 mg Maximum cumulative dose: 2,500 mg	Oral iron (n=63)
	VIT-IV-CL-003	46	Repeated doses until iron repletion using total iron requirement calculation. 500 mg or 1000 mg per dose Maximum total dose: 2000 mg	None
Non-dialysis dependent chronic kidney disease	1VIT04004	147	Repeated doses until iron repletion using total iron requirement calculation. Maximum single dose: 1000 mg Maximum cumulative dose: 2,500 mg	oral iron (n=103)
	1VIT05005 (extension of 1VIT04004: All patients including oral iron arm in 04004 are eligible to enroll in this study)	127 (52 new patients and 75 patients received Injectafer in 1VIT04004)	44-week extension long-term safety study. Repeated doses until iron repletion using total iron requirement calculation. Maximum single dose: 1000 mg	None
Hemodialysis	VIT-IV-CL-015	119	200 mg two or three times weekly until total iron required for iron repletion Maximum cumulative dose: 2,500 mg	Venofer (n=118)
	VIT-53214	162		None
Chronic heart failure	FER-CARS-01	30	200 mg weekly until total iron required for iron repletion	Venofer (n=27) Placebo (n=15)
Total number of exposed patients		**2080 Single dose studies: 614 Repeated dose studies: 1466**		**Oral Iron: 834 Venofer: 145 Placebo: 592**

5.1 Extent of Exposure

All multi-center Studies

Among the 1998 subjects treated with Injectafer in the multicenter studies (584 from crossover study VIT-5006 and 1414 from the remaining 11 phase 2/3 multicenter studies), the majority of the subjects received only 1 (36.2%) or 2 (43.1%) doses of Injectafer, ranging from 1 to 11 doses. The mean total dose of Injectafer received was 1270.1 (±371.65) mg and the mean maximum single dose received was 811.2(± 287.61) mg (see table below).

Summary of Extent of Exposure to Injectafer (All Multi-center Studies)

	FCM
Number of Infusions	(N=1998)
1[a]	723 (36.2%)
2	862 (43.1%)
3	104 (5.2%)
4	16 (0.8%)
5	30 (1.5%)
6	97 (4.9%)
7	86 (4.3%)
8	52 (2.6%)
9	18 (0.9%)
10	7 (0.4%)
11	3 (0.2%)
Total Dose of Iron (mg) Received	(N=1998)
Mean (SD)	1270.1 (371.65)
Median	1200
Minimum[a] - Maximum	0.0-3400.0
Maximum Single Dose (mg)	(N=1998)
Mean (SD)	811.2 (287.61)
Median	1000
Minimum[a] - Maximum	0.0-1000.0

All Multicenter Studies: GI: VIT-IV-CL-003 and VIT-IV-CL-008; Postpartum: VIT-IV-CL-009, 1VIT03001, and 1VIT06011; HUB: 1VIT04002/1VIT04003; HD: VIT-IV-CL-015 and VIT-53214; NDD-CKD: 1VIT04004; IDA: 1VIT05006; CHF: FER-CARS-01.
SD = Standard Deviation
a Subjects with 0 mg total dose are listed under the 1 infusion category.
Cross-reference: Appendix Table 2.1

Study 1VIT05005 (extension study)

Study 5005 was a 44 week extension (with no active control) to Study lVIT04004 (VIT-4004), a study conducted among patients with chronic kidney disease. Study 5005 is listed as unique from the other multi-center studies since it is an extension study that followed another study.

The mean number of doses received during the study was 3.0 (±1.4) for erythropoietin (EPO) users and 2.3 (± 1.5) for non-EPO users. The mean exposure during the study, calculated as the total dose of study drug administered, was 1791.4 (±859.0) mg for EPO

users and 1459.6 (± 991.0) mg for non-EPO users. The average days between doses was 71.2 (±38.2) for EPO users and 85.1 (±44.6) for non-EPO users.

5.2 Demographic Characteristics

The demographic characteristics of study patients in the multi-center studies by treatment group are shown in the table below. The majority of study patients were female (83.1%) and Caucasian (59.3%) with a mean of 40.2 years.

Demographic characteristics in the multi-center studies

	FCM (N=1414)	Oral Iron (N=834)	Venofer (N=145)	Placebo (N=15)	Crossover Study (N=594)	Total (N=3002)
Sex						
Male	292 (20.7%)	55 (6.6%)	81 (55.9%)	8 (53.3%)	70 (11.8%)	506 (16.9%)
Female	1122 (79.3%)	779 (93.4%)	64 (44.1%)	7 (46.7%)	524 (88.2%)	2496 (83.1%)
Race						
Asian	187 (13.2%)	158 (18.9%)	0	0	4 (0.7%)	349 (11.6%)
Black	207 (14.6%)	174 (20.9%)	0	0	110 (18.5%)	491 (16.4%)
Caucasian	880 (62.2%)	371 (44.5%)	145 (100.0%)	15 (100.0%)	368 (62.0%)	1779 (59.3%)
Hispanic	96 (6.8%)	118 (14.1%)	0	0	101 (17.0%)	315 (10.5%)
Other	44 (3.1%)	13 (1.6%)	0	0	11 (1.9%)	68 (2.3%)
Age (years)						
Mean (SD)	39.9 (16.19)	36.5 (15.75)	54.1 (14.98)	69.7 (11.55)	42.3 (16.72)	40.2 (16.66)
Median	36.0	32.0	53.0	74.0	40.0	36.0
Minimum - Maximum	15.0-89.0	15.3-89.0	22.0-84.0	48.0-88.0	18.0-89.0	15.0-89.0
≥65	139 (9.8%)	74 (8.9%)	40 (27.6%)	12 (80.0%)	70 (11.8%)	335 (11.2%)
≥75	61 (4.3%)	39 (4.7%)	16 (11.0%)	7 (46.7%)	37 (6.2%)	160 (5.3%)
Weight (kg)	N=1413	N=833	N=145	N=15	N=594	N=3000
Mean (SD)	71.4 (19.33)	74.7 (22.43)	70.8 (13.69)	72.4 (11.25)	80.6 (20.67)	74.1 (20.54)
Median	67.6	69.0	71.0	70.2	78.0	70.0
Minimum - Maximum	28.3-171.5	35.0-184.2	39.4-107.0	60.0-100.2	35.4-175.1	28.3-184.2
≤ Median	812 (57.4%)	431 (51.7%)	70 (48.3%)	7 (46.7%)	200 (33.7%)	1520 (50.6%)
> Median	601 (42.5%)	402 (48.2%)	75 (51.7%)	8 (53.3%)	394 (66.3%)	1480 (49.3%)

All Active-Controlled Multi-center Studies

In the active-controlled multi-center studies, the demographic characteristics were similar between the Injectafer (FCM) and oral iron groups, while the Venofer group had a greater proportion of males than females and the mean age was higher (54.1 years Venofer) compared to the FCM and oral iron groups (36.5 to 39.1 years), differences that may relate to the smaller sample size and the nature of the subject population.

Demographic characteristics in the active-controlled multi-center studies

	FCM (N=1206)	Oral Iron (N=834)	Venofer (N=145)	Placebo (N=15)	Total (N=2200)
Sex					
Male	191 (15.8%)	55 (6.6%)	81 (55.9%)	8 (53.3%)	335 (15.2%)
Female	1015 (84.2%)	779 (93.4%)	64 (44.1%)	7 (46.7%)	1865 (84.8%)
Race					
Asian	182 (15.1%)	158 (18.9%)	0	0	340 (15.5%)
Black	187 (15.5%)	174 (20.9%)	0	0	361 (16.4%)
Caucasian	722 (59.9%)	371 (44.5%)	145 (100.0%)	15 (100.0%)	1253 (57.0%)
Hispanic	96 (8.0%)	118 (14.1%)	0	0	214 (9.7%)
Other	19 (1.6%)	13 (1.6%)	0	0	32 (1.5%)
Age (years)					
Mean (SD)	39.1 (16.65)	36.5 (15.75)	54.1 (14.98)	69.7 (11.55)	39.3 (16.89)
Median	34.3	32.0	53.0	74.0	34.1
Minimum - Maximum	15.0-89.0	15.3-89.0	22.0-84.0	48.0-88.0	15.0-89.0
≥65	136 (11.3%)	74 (8.9%)	40 (27.6%)	12 (80.0%)	262 (11.9%)
≥75	61 (5.1%)	39 (4.7%)	16 (11.0%)	7 (46.7%)	123 (5.6%)
Weight (kg)	N=1205	N=833	N=145	N=15	N=2198
Mean (SD)	71.5 (19.96)	74.7 (22.43)	70.8 (13.69)	72.4 (11.25)	72.7 (20.60)
Median	67.0	69.0	71.0	70.2	68.0
Minimum - Maximum	28.3-171.5	35.0-184.2	39.4-107.0	60.0-100.2	28.3-184.2
≤ Median	634 (52.6%)	394 (47.2%)	65 (44.8%)	7 (46.7%)	1100 (50.0%)
> Median	571 (47.3%)	439 (52.6%)	80 (55.2%)	8 (53.3%)	1098 (49.9%)

All Active-Controlled Multicenter Studies: GI: VIT-IV-CL-008; Postpartum: VIT-IV-CL-009, IVIT03001, and IVIT06011; HUB: IVIT04002/IVIT04003; HD: VIT-IV-CL-015; NDD-CKD: IVIT04004; CHF: FER-CARS-01.

Baseline characteristics for the data pool referred to as "All calculated dose/first dose 1,000 mg studies" showed similar distribution of characteristics between subjects in the Injectafer group and those in the oral iron group. This data pool is especially relevant to consideration of the proposed market population since the control treatment is only oral iron and studies of less than the potential 1,000 maximum first Injectafer dose are excluded.

5.3 Deaths

All completed clinical studies

Eleven deaths were reported in all completed clinical studies. Ten occurred in Injectafer-treated patients, one death occurred in a Venofer-treated patient, and no deaths occurred in oral iron-treated patients. The nominal overall mortality rate was 0.48% (10/2080) in Injectafer-treated patients as compared to 0.06% (1/1571) in control-treated patients.

Overall mortality in all clinical studies by treatment group

	Number of patients*	Deaths	Mortality
Injectafer	2080	10	0.48%
Control	1571	1	0.06%

*Including 584 patients in Injectafer group and 569 patients in the control group from a cross-over placebo-controlled study

Randomized controlled clinical studies

Seven deaths were reported from randomized controlled clinical studies and four were reported from uncontrolled single arm studies. The nominal mortality rate was 0.33% (6/1814) in Injectafer-treated patients as compared to 0.06% (1/1571) in control-treated patients in these randomized studies (see table below).

Mortality in randomized clinical studies by treatment group

	Number of patients*	Deaths	Mortality
Injectafer	1814	6	0.33%
Control	1571	1	0.06%

*Including 584 patients in Injectafer group and 569 patients in the control group from a cross-over placebo-controlled study

By Injectafer dosing regimen

Mortality rate by Injectafer dose regimen in all completed studies is shown below. Seven deaths (0.4%) were reported in the Injectafer group as compared to none (0%) in the control group for the proposed "first-dose maximum of 1000 mg" dosing regimen studies.

Mortality rate by Injectafer dose regimen in all clinical studies

Injectafer dose regimen	Injectafer	Control
First-dose 1000 mg (proposed for label)	7/1769 (0.4%)	0/1411 (0.0%)
200 mg 2-3 times per week (Hemodialysis patients)	3/281 (1.1%)	0/118 (0.0%)
200 mg per week (chronic heart disease patients)	0/30 (0.0%)	1/42 (2.4%)

Mortality rate by Injectafer dose regimen in all randomized controlled studies is shown below.

Mortality rate by Injectafer dose regimen in all randomized controlled clinical studies

Injectafer dosing regimen	Injectafer	Control
First-dose 1000 mg (proposed)	5/1665 (0.3%)	0/1411 (0.0%)
200 mg 2-3 times per week	1/119 (0.8%)	0/118 (0.0%)
200 mg per week	0/30 (0.0%)	1/42 (2.4%)

By each study

The 10 deaths in the Injectafer group were reported from seven studies in four different populations, as previously noted. One death in the control group was reported in the Venofer treatment group in the pilot study (FER-CARS-01) in patients with chronic heart failure.

The following tables show deaths occurred in randomized controlled studies and in uncontrolled studies.

Deaths in randomized controlled studies

Study populations	Injectafer group	Control group (Oral iron/Venofer/placebo)
Post-partum anemia		
1 VIT03001	1/174 (0.5%)	0/178 (0%)
VIT-IV-CL-009	0/227	0/117
1VIT06011	0/142	0/147
Heavy uterine bleeding		
1 VIT-4002/4003	0/230	0/226
Inflammatory bowel disease		
VIT-IV-CL-008	1/137 (0.7%)	0/63 (0%)
Hemodialysis		
VIT-IV-CL-015	1/119 (0.8%)	0/118 (0%) (Venofer)
Single dose safety studies in patients with iron deficiency anemia		
1VIT05006 (cross-over study)	1/584 (0.2%)	0/569 (0%) (placebo)
VIT-IV-CL-02	0/24	0/8
Non-HD CKD		
1VIT04004	2/147 (1.4%)	0/103 (0%)
Chronic heart failure		
FER-CARS-01	0/30	1/27 (3.7%) (Venofer) 0/15 (placebo)
Overall	6/1814 (0.33%)	1/1571 (0.06%)

Deaths in Uncontrolled Studies

Study Populations	Injectafer
Inflammatory bowel disease	
VIT-IV-CL-003	0/46 (0%)
Hemodialysis	

VIT-53214	2/162 (1.2%)
Single dose safety study	
VIT-IV-CL-001	0/6 (0.0%)
Non-HD CKD	
1VIT05005	2/127 (1.6%)
Total	4/341(1.2%)

Cause of death, time relationship with Injectafer treatment and dose received

Determination of the cause of death in clinical studies is vulnerable to imprecision and subjectivity in assessment. Based upon the information supplied from site investigators, the FDA review team regards the main causes of death in the Injectafer group as due to cardiac disorders in five cases (two cardiac arrests, one anterior myocardial infarction, one heart failure and one cardiac "insufficiency"), three cases due to infections (sepsis, abscess), one case due to gastrointestinal bleeding and one case due to a motor-vehicle accident.

The cause of death in Venofer control group was assessed as worsening heart failure.

Among the 10 patients who died in the Injectafer group, five received a single dose of Injectafer (four received 1000 mg and one received 200 mg) and five received two or more doses of Injectafer. All events leading to deaths except one occurred within 32 days of Injectafer last injection.

The patient who died in the Venofer group received Venofer 200 mg for two doses and died five days after the last injection.

The following tables summarize deaths in randomized controlled studies and in uncontrolled studies.

Deaths in Randomized Controlled Studies

Populations/ Studies	ID# Age/ Gender	Causes of deaths per investigator	Time since last dose	Injectafer dose
Post-partum anemia 1VIT03001	ID 106-247 27/F	Peripartal cardiomyopathy with heart failure	8 days	1000 mg Single dose
Hemodialysis VIT-IV-CL-015	ID 15-29-018 58/M	Acute anterior MI	4 days	200 mg Single dose

Inflammatory bowel disease VIT-IV-CL-008	ID 8-63-013 56/M	Cardiac arrest	1 day	1000 mg Single dose
Cross-over safety study 1VIT05006	ID 602-30274 48/F	Pneumonia, respiratory failure, sepsis	27 days	1000 mg Single dose
Non-HD CKD 1VIT04004	ID 432-216 85/M	Urosepsis	32 days	1000 mg single dose
	ID 502-337 76/ M	Multiple trauma secondary to a MVA	14 days	1000 mg and 500 mg x 2 doses
Chronic heart failure FER-CARS-01	ID 01 72/F	Worsening heart failure	5 days	Venofer 200 mg for 2 doses

Deaths in Uncontrolled Clinical Studies

Populations/ Studies	Age/ Gender	Causes of deaths per investigator	Time since last dose	Injectafer/Venofer dose
Hemodialysis VIT-53214	ID 1-21-003 59/F	Shortness of breath, Respiratory insufficiency (acute cardiac insufficiency per hospital discharge summary)	15 days	Injectafer 200 mg for 6 doses
	ID 1-35-003 54/F	Cardio-respiratory arrest	19 days	Injectafer 200 mg for 8 doses
Non-HD CKD VIT05005 (extension of 1VIT04004)	ID 422-224 86/M	Colonic (sigmoid) perforation, abscess	88 days	Injectafer 1000 mg and 500 mg
	ID 428-245 64/F	Anoxic encephalopathy, GI bleeding	30 days	Injectafer 1000 mg for 2 doses followed by 500 mg

Death narratives:

The following are summary narratives for the 11 deaths.

Injectafer group:

Case 1 (death in a study of post-partum patients):

A 27-year-old female had hemoglobin level of 7.9 g/dL with a TSAT of 5% and ferritin of 5.6 ng/mL 3 days after an uncomplicated vaginal delivery on . She was enrolled in Study 1 VIT03001 at a US site. Her past history was reportedly significant for anemia that required a blood transfusion during a pregnancy in . Her laboratory data, other than hematologic parameters consistent with iron deficiency anemia, were unremarkable. She received her first dose of Injectafer 1000 mg on . On 5 she did not keep her appointment with the clinic. On a friend found her unresponsive at her home in bed with "frothy edema fluid" from her mouth. Emergency response attendants could not resuscitate her and she was pronounced dead on arrival at the hospital.

An autopsy was done with the following summary findings: dilated left ventricle, no significant inflammatory cell infiltrate or fibrosis noted, moderate bilateral pleural effusions, pulmonary edema, and soft tissue edema. Blood alcohol was negative. The cause of death was listed as peripartal cardiomyopathy with heart failure. The investigator considered this serious adverse event (peripartal cardiomyopathy with heart failure) unrelated to the study drug.

In the summary/interpretation section of the autopsy it is written "It is my opinion that death resulted from peripartal cardiomyopathy with heart failure. This entity is represented by left ventricle dilatation and heart failure and may develop in the late stages of pregnancy or the first six months postpartum. The incidence of this cardiomyopathy is 10 in 100,000 births and the mortality is between 5 and 60%."

Hb at baseline was 7.9 g/dL and no values were reported thereafter.
Phosphate at baseline was 3.9 mg/dL and no values were reported thereafter. The sponsor's "projected lowest" phosphate was >2 mg/dL at day 7 post-dose.

Case 2 (death in a study of patients with chronic kidney disease):

A 58-year-old male had a medical history of type 2 diabetes mellitus with complications of hypertension and chronic renal failure had been on hemodialysis since . He was enrolled in Study VIT-IV-CL-015 and received his first dose of Injectafer 200 mg on . Later that day, the patient experienced clotting in blood lines at the end of a hemodialysis session. This event was considered to be a mild intensity but the study medication was discontinued on the same day. On , the patient was admitted to an intensive care unit for severe chest pressure, accompanied by nausea and sweating and was diagnosed with acute extensive anterior myocardial infarction with ST elevation. The patient developed congestive heart failure and subsequently died on . No autopsy was performed. This event was considered unlikely to be related to study drug by the site investigator.

Concomitant medication included diltiazem R, Micardis (telmisartan), Antistenocardin (dipyridamole), aspirin, Teveten (eprosartan), Insulin, and Glucosae, Eprex (epoetin alfa), paracetamol and Biseptol.

Hb was 9.3 g/dL on and 7.8 g/dL on
No serum phosphate data were available.

Case 3 (death in a study of patients with inflammatory bowel disease):

A 56-year old male had a medical history of aortic valve stenosis and mitral insufficiency, ulcerative colitis and anemia. The patient was enrolled in Study VIT-IV-CL-008. The patient's Hb was 5.5 g/dL with TSAT 2% and ferritin 14 ng/mL on screening. He received his only dose of Injectafer 1000 mg on at 8 am and at this time his Hb was 4.8 g/dL. On at 10 a.m., the patient experienced cardiac arrest at the work place. Resuscitation measures were initiated in the ambulance and the patient died on the way to hospital. According to the investigator the cause of death was due to underlying cardiac disease and was considered to be unrelated to study drug. No autopsy was performed. No further information on the case is available.

Concomitant medication included Salofalk (mesalazine) for ulcerative colitis.

Hb was 5.5 g/dL on and 4.8 g/dL on
No serum phosphate data were available.

Case 4 (death in the cross-over safety study):

A 48 year-old female had a medical history of anemia, gastric bypass for morbid obesity, depression, recurrent UTI, and hysterectomy. She was enrolled in a single dose cross-over safety study 1VIT05006. Her Hb was 11.4 g/dL with TSAT 4% and ferritin 5 ng/mL on She received placebo on and Injectafer 1000 mg on Her Hb was 10.8 g/dL prior dosing on . On , the patient complained of right earache and was prescribed Cortisporn OTIC and hydrocodone for 5 days for ear infection. She presented to the physicians office on with a sore throat, cough, and stuffy nose. Her vital signs were recorded as T 97.2° F, pulse 94, blood pressure 118/70, and oxygen saturation 97%. A Strep test was negative. Urine showed positive nitrates and trace of leukocytes. She was diagnosed with UTI and URI and prescribed Augmentin 875 mg BID for 10 days. Her Hb was 11.8 g/dL on . On her case worker called the ambulance to transport her to the emergency room because of shortness of breath, coughing, weakness, and fatigue. She presented with severe respiratory distress with hypoxemia (O2 saturation 60%), tachycardia (130's), and systolic BP 80's on arrival in ER. Chest x-ray showed extensive infiltrate involving the right lung, presumably due to pneumonia. She was intubated for respiratory failure. Soon the patient developed bradycardia and hypotension and went into cardiac arrest. The patient died in the ER less than 2 hours after arrival. Her laboratory data showed WBC 1700 with 14% band and Hb 14.1. Sputum and 2 blood cultures were positive for *Aeromonas hydrophila*. Cardiac enzymes on admission were normal without additional follow-up. The initial diagnoses by ER physician were "pneumonia, hypoxia, respiratory failure, sepsis, acidosis, and acute renal failure". No autopsy was performed.

The investigator listed the AE as pneumonia and considered it as a serious adverse event and to be unrelated to study drug.

Hb: 11.4 g/dl on , 11.8 g/dL on , and 14.1 on
Serum phosphate was reported as 3.3 mg/dL on and 2.7 mg/dL on

Case 5 (death in a study of patients with chronic kidney disease):

An 85 year-old male had a medical history of chronic kidney disease, atrial fibrillation, CAD with MI, prostate cancer, and pneumonia. He received a single dose of Injectafer 1000 mg on and his Hb was 10.2 g/dL on He was admitted to the hospital on for weakness, fever and difficulty urinating. In the ER, his temperature was 102.3°, heart rate 140, BP 118/73, respiratory rate of 30 and O2 sat 94% on room air. EKG revealed atrial fibrillation with rapid ventricular response (129 beats per minute), and non-specific ST-T wave abnormality. A chest x-ray showed "no interim changes" in the appearance of the chest based on radiologist report. His laboratory data showed Hb 10.4, BUN 38, creatinine 3.2. Retroperitoneal ultrasound performed the next day showed bladder outlet obstruction with bilateral moderate hydronephrosis, chronic renal disease, mild ascites, and right pleural effusion. Urine and blood cultures grew methicillin resistant staph aureus (MRSA). According to the sponsor, the patient was treated with IV fluids and antibiotics and his condition continued to deteriorate with dropping blood pressures. The family and patient decided that they did not want dialysis or medications to support his blood pressure and he was discharged to hospice care on and died on the same day. No autopsy was performed.

The investigator listed this event as urosepsis and considered it as a serious adverse event and unrelated to study drug.

Hb was 10.2 g/dL on , 10.4 g/dL on and 8.1 g/dL on .
Phosphate was 4.3 mg/dL on and 2.6 mg/dL on .

Case 6 (death in a study of patients with chronic kidney disease):

A 76-year-old male had a medical history of chronic kidney disease, a ruptured abdominal aortic aneurysm in , hypertension, hemi-laminectomy and peptic ulcer disease was randomized in the 1VIT04004 study. He received his first dose of Injectafer (1000 mg) IV on . His second dose (500 mg) was given on . His third and final dose (500 mg) was given . On (14 days after his last dose), he received multiple injuries in a motor vehicle accident. He died of multiple injuries on His wife died at the scene of the accident from multiple injures.

The investigator considered this serious adverse event (multiple traumas due to MVA) unrelated to study drug.

Laboratory data:

Hb was 10.4 g/dl on , 10.3 g/dl on , 10.8 g/dl on and 11.9 g/dl on
No serum phosphate values < 2 mg/dL were reported.

Case 7 (death in a study of patients with chronic kidney disease):

A 59-year-old Caucasian female had a medical history of tuberculosis of the lung, chronic bronchitis, chronic renal failure on hemodialysis, hypertension, and chronic persistent hepatitis B. The patient was enrolled in Study 53214. The patient's Hb was 8.1 d/dL with TSAT 4% and ferritin 116 ng/mL at baseline. She received her first dose of Injectafer 200 mg on , and additional 5 doses of 200 mg in subsequent sessions of hemodialysis. The last dose was on . On , she had an abnormal chest x-ray, which was considered by the investigator to be non-serious, of moderate intensity and unrelated to study drug. On , she was admitted to hospital with cough, weakness and dyspnea after physical exercise and a chest radiograph disclosed findings consistent with tuberculosis (TB). The patient was admitted for treatment for TB. On hospital record of discharge summary, in Results of Treatment section, it stated "on developed acute cardiac insufficiency, and at 21:30 patient died". On CRF, the primary cause of death listed as "shortness of breath, respiratory insufficiency" by the investigator. No detailed hospital records were submitted. No autopsy was performed.

This event was considered by the investigator to be serious, of severe intensity and unrelated to study drug.

Concomitant medication included calcium carbonate for renal osteoporosis, and Eprex (epoetin alfa) for renal anemia.

Hb was 8.1 g/dL on , 7.6 g/dL on , and 9.1 g/dL on
The sponsor reported no serum phosphate levels.

Case 8 (death in a study of patients with chronic kidney disease):

A 54-year-old female had a medical history of hypertension, congestive heart failure, chronic renal failure on hemodialysis, uremic cardiopathy, and pericarditis. The patient was enrolled in Study 53214. The patient's Hb was 6.0 g/dL with TSAT 9% and ferritin 39 ng/ml at baseline. She received the first dose of Injectafer 200 mg on and additional 7 doses of Injectafer 200 mg during subsequent hemodialysis. The last dose was on ECGs performed on and again during were considered abnormal, but not clinically significant. The patient died at home on On the translation of the medical certificate of death issued by a family doctor, heart failure was listed as the direct cause of death, atrial fibrillation was listed as with preceding causes of death, and hypertension was listed as initial morbidity.

The investigator stated that patient "deceased suddenly at home" and "We found out about her death by calling the patient when she failed to come for scheduled dialysis

session" on a letter to the sponsor dated on The sponsor stated "Patient died due to cardio-respiratory arrest" in another letter to the sponsor dated On the case report form, cardiorespiratory arrest was listed as the primary cause of death and acute heart failure/atrial fibrillation was listed as underlying cause of death. The investigator considered the death was not related to the study drug. An autopsy was not performed.

Concomitant medication included dipyridamole for anti-aggregation, dicarbocalm (from) as prophylaxis of hyperphosphatemia, nifedipine and metoprolol (from) for hypertension, folic acid (from) as prophylaxis of hyperhomocysteinemia, and multivitamins (from) as prophylaxis of hypovitaminosis.

Hb was 6.0 g/dL on , 7.6 g/dL on , and 10.1 g/d on
The sponsor reported no serum phosphate levels.

Case 9 (death in a study of patients with chronic kidney disease):

An 86-year-old male had a medical history of chronic kidney disease, coronary artery disease, hypertension, diabetes type 2, and arthritis. He was randomized originally to ferrous sulfate 325mg during the 1VIT04004 study. He continued on the 1VIT05005 extension study and received a total dose of 1,500 mg of Injectafer. He received his first dose of Injectafer (1000 mg IV) on the second dose of 500 mg on He was admitted to the hospital on for not feeling well and a report of being "unresponsive" at times with decreased appetite. Upon arrival to the ER his temperature was 97.6, pulse 102, BP 86/42, respiratory rate of 20, and pulse oximetry of 96% on 2 L. The Hb was 9.4 g/dl. EKG revealed atrial fibrillation with right bundle branch block, rate 141 beats per minute with no ST-T wave abnormality. Chest x-ray showed free intraperitoneal air, suggesting bowel perforation. The patient was admitted to the ICU, received several units of blood, and had an exploratory laparotomy and sigmoid resection with colostomy on . On , the patient died. No detailed information and no discharge summary were provided.

The investigator listed this event as perforation of colon and considered this event is serious and unrelated to study drug.

Death certificate issued on listed the causes of the death as bowel obstruction, cardiomyopathy, coronary artery disease and renal insufficiency.

Hb was 9.8 g/dL on , 10.4 g/dL on , and 9.4 g/dl on
Serum phosphate was 3.4 mg/dL on 3.1 mg/dL on and 3.2 mg/dL on

Case 10 (death in a study of patients with chronic kidney disease):

A 64-year-old female had a medical history of chronic kidney disease, diabetes type 2, hypertension, and hyperlipidemia. She was randomized in the 1VIT04004 study to the

Injectafer arm on and continued on the 1VIT05005 extension study. She received Injectafer 1,000 mg on during the 1VIT04004 study. She continued on the extension study and received an additional 1,500 mg of Injectafer (500 mg each on and , and the last dose of 500 mg on . On , she was admitted to the hospital for an exploratory laparotomy. Pathology report of the mesenteric lymph nodes revealed granulomatous lymphadenitis. AFB and GMS stains were negative for organism and tissues were sent for routine culture of fungal and mycobacterial organism. Her Hb was 9.7 g/dl on admission. She began having gastrointestinal bleeding on , with hemodynamic instability on . Later the patients had sudden loss of consciousness and drop of blood pressure and went to cardiac arrest. Resuscitation was initiated and she was intubated. She was transfused with 9 more units of PRBCs and endoscopy found the massive GI bleed secondary to stress gastritis. Hypoxic encephalopathy was diagnosed on The patient remained in persistent vegetative state and on the family elected to withdraw life support and the patient died. The sponsor attributed the cause of death to anoxic encephalopathy. No autopsy was performed. Only a hospital discharge summary was provided and no detailed hospital records for the last admission were provided.

The event was attributed to fatal gastrointestinal bleeding and the site investigator considered this event unrelated to the study drug on the CRF.

Hb was 10.7 g/dL on 11.8 g/dL on and 11.6 g/dL on
Serum phosphate was 4.2 mg/dl on 4.6 mg/dL on and 4.5 mg/dL on .

Venofer group:

Case 1 (death in a study of patients with chronic heart failure):

A 72 year-old female with chronic heart failure, renal failure and anemia was randomized in chronic heart failure trial (FER-CARS-01) on Her medical history was significant for arterial hypertension, angina pectoris, myocardial infarction, thromboembolus of the pulmonary artery, atrial fibrillation, chronic pyelonephntis, peptic ulcer, heart failure, and renal failure (GFR 40.9 mL/min). Her physical exam on demonstrated cardiomegaly, atrial fibrillation and a systolic murmur. There were crackles in her lungs and she complained of dyspnea. She also presented with pitting edema of the legs. Her NYHA class was IV (unable to carry out any physical activity without fatigue or dyspnea). ECG that was done showed atrial fibrillation and left bundle branch block. Her total iron requirement was calculated to be 800mg.

She received her first dose of blinded study medication 200 mg IV on She experienced a short period of "heating in the head for *5* minutes following the medication. She received her second dose of study medication on No adverse events were noted on this day of dosing. ECG done on indicated an increase in the QT interval. On her family reported that she had increased dyspnea and edema. Her heart failure worsened and she died on No

Autopsy was performed. When the study blind was broken the study drug for this patient was confirmed to be Venofer.

The investigator considered the serious adverse event (worsening heart failure) unrelated to study drug.

5.4 Serious Adverse Events, Especially "Cardiac" Events

As noted before, data from the clinical studies may be "pooled" in various methods. However, the bulk of clinical data are derived from studies that compared Injectafer to oral iron and these data are especially pertinent since oral iron would be an alternative treatment option for patients (ie., the proposed indication is not limited to patients who are intolerant of oral iron).

Within the active-controlled, multicenter studies, a serious adverse event was reported by 3.6% of Injectafer-treated patients and 2.5% of patients receiving oral iron. Serious "cardiac" events were reported in 1.1% of Injectafer-treated patients and 0.4% of patients receiving oral iron. These data are summarized in the reprint of the sponsor's table (below).

Serious adverse events experienced by ≥ 2 subjects in any group by system organ class, preferred term and treatment group in active-controlled, multicenter studies

SOC Preferred Term	FCM (N=1206)	Oral Iron (N=834)	Venofer (N=145)	Placebo (N=15)
At Least 1 Serious Adverse Event	43 (3.6%)	21 (2.5%)	13 (9.0%)	2 (13.3%)
Cardiac disorders	13 (1.1%)	3 (0.4%)	4 (2.8%)	1 (6.7%)
Cardiac failure	2 (0.2%)	0	3 (2.1%)	1 (6.7%)
Cardiac failure congestive	2 (0.2%)	2 (0.2%)	0	0
Coronary artery disease	2 (0.2%)	0	0	0
Myocardial infarction	3 (0.2%)	0	0	0
Gastrointestinal disorders	6 (0.5%)	4 (0.5%)	2 (1.4%)	0
Gastrointestinal haemorrhage	1 (0.1%)	2 (0.2%)	2 (1.4%)	0
Melaena	0	0	2 (1.4%)	0
Infections and infestations	11 (0.9%)	3 (0.4%)	2 (1.4%)	0
Endometritis	0	2 (0.2%)	0	0
Pelvic abscess	0	2 (0.2%)	0	0
Sepsis	2 (0.2%)	0	0	0
Renal and urinary disorders	0	3 (0.4%)	0	1 (6.7%)
Renal failure chronic	0	2 (0.2%)	0	0
Reproductive system and breast disorders	3 (0.2%)	1 (0.1%)	0	0
Uterine haemorrhage	2 (0.2%)	1 (0.1%)	0	0

All Active-Controlled Multicenter Studies: GI: VIT-IV-CL-008; Postpartum: VIT-IV-CL-009, 1VIT03001, and 1VIT06011; HUB: 1VIT04002/1VIT04003; HD: VIT-IV-CL-015; NDD-CKD: 1VIT04004; CHF: FER-CARS-01.

In oral-iron controlled trials ("all calculated dose/first dose 1,000 mg studies"), the overall incidence of serious adverse events was 3.2% in the Injectafer group and 2.5% in the oral iron group as shown below in the sponsor's excerpted table. These data are especially relevant since baseline characteristics were similar between the two study groups and the dose regimen is the one proposed for marketing.

Treatment-Emergent Serious AEs by System Organ Class, Preferred Term, and Treatment Group
(All Calculated Dose/First-Dose 1,000 mg Studies)
Safety Population

	FCM (N=1057)	Oral Iron (N=834)
AT LEAST ONE ADVERSE EVENT	34 (3.2%)	21 (2.5%)
CARDIAC DISORDERS	9 (0.9%)	3 (0.4%)
CARDIAC ARREST	1 (0.1%)	0 (0.0%)
CARDIAC FAILURE	1 (0.1%)	0 (0.0%)
CARDIAC FAILURE CONGESTIVE	2 (0.2%)	2 (0.2%)
CORONARY ARTERY DISEASE	2 (0.2%)	0 (0.0%)
MITRAL VALVE PROLAPSE	1 (0.1%)	0 (0.0%)
MYOCARDIAL INFARCTION	1 (0.1%)	0 (0.0%)
MYOCARDIAL ISCHAEMIA	0 (0.0%)	1 (0.1%)
PALPITATIONS	1 (0.1%)	0 (0.0%)
TACHYCARDIA	1 (0.1%)	0 (0.0%)
GASTROINTESTINAL DISORDERS	6 (0.6%)	4 (0.5%)
ABDOMINAL PAIN	0 (0.0%)	1 (0.1%)
COLITIS ULCERATIVE	1 (0.1%)	0 (0.0%)
CROHN'S DISEASE	1 (0.1%)	0 (0.0%)
GASTROINTESTINAL HAEMORRHAGE	1 (0.1%)	2 (0.2%)
HAEMORRHOIDS	1 (0.1%)	0 (0.0%)
INTESTINAL HAEMORRHAGE	0 (0.0%)	1 (0.1%)
PANCREATITIS ACUTE	1 (0.1%)	0 (0.0%)
SMALL INTESTINAL HAEMORRHAGE	1 (0.1%)	0 (0.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (0.2%)	0 (0.0%)
CHEST PAIN	1 (0.1%)	0 (0.0%)
PYREXIA	1 (0.1%)	0 (0.0%)
HEPATOBILIARY DISORDERS	3 (0.3%)	1 (0.1%)
AUTOIMMUNE HEPATITIS	1 (0.1%)	0 (0.0%)
CHOLECYSTITIS	1 (0.1%)	0 (0.0%)
CHOLECYSTITIS ACUTE	1 (0.1%)	0 (0.0%)
CHOLELITHIASIS	0 (0.0%)	1 (0.1%)
INFECTIONS AND INFESTATIONS	10 (0.9%)	3 (0.4%)
APPENDICITIS	1 (0.1%)	0 (0.0%)
CELLULITIS	1 (0.1%)	0 (0.0%)
ENDOMETRITIS	0 (0.0%)	2 (0.2%)
ENDOMETRITIS DECIDUAL	1 (0.1%)	0 (0.0%)
PELVIC ABSCESS	0 (0.0%)	2 (0.2%)
PELVIC INFLAMMATORY DISEASE	1 (0.1%)	0 (0.0%)
POSTOPERATIVE INFECTION	1 (0.1%)	0 (0.0%)
PYELONEPHRITIS	1 (0.1%)	0 (0.0%)
SEPSIS	2 (0.2%)	0 (0.0%)
SKIN INFECTION	1 (0.1%)	0 (0.0%)
UPPER RESPIRATORY TRACT INFECTION	1 (0.1%)	0 (0.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (0.2%)	0 (0.0%)
POLYTRAUMATISM	1 (0.1%)	0 (0.0%)
POSTOPERATIVE FEVER	1 (0.1%)	0 (0.0%)
METABOLISM AND NUTRITION DISORDERS	1 (0.1%)	1 (0.1%)
ELECTROLYTE DEPLETION	1 (0.1%)	0 (0.0%)
HYPERKALAEMIA	0 (0.0%)	1 (0.1%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	3 (0.3%)	1 (0.1%)
COLON CANCER	1 (0.1%)	0 (0.0%)
OVARIAN CANCER	1 (0.1%)	0 (0.0%)
RECTAL CANCER	1 (0.1%)	0 (0.0%)
UTERINE LEIOMYOMA	0 (0.0%)	1 (0.1%)

NERVOUS SYSTEM DISORDERS	0 (0.0%)	2 (0.2%)
CEREBROVASCULAR ACCIDENT	0 (0.0%)	1 (0.1%)
TRANSIENT ISCHAEMIC ATTACK	0 (0.0%)	1 (0.1%)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	1 (0.1%)	0 (0.0%)
PERIPARTUM CARDIOMYOPATHY	1 (0.1%)	0 (0.0%)
PSYCHIATRIC DISORDERS	0 (0.0%)	1 (0.1%)
MAJOR DEPRESSION	0 (0.0%)	1 (0.1%)
RENAL AND URINARY DISORDERS	0 (0.0%)	3 (0.4%)
GLOMERULONEPHRITIS PROLIFERATIVE	0 (0.0%)	1 (0.1%)
RENAL FAILURE CHRONIC	0 (0.0%)	2 (0.2%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	3 (0.3%)	1 (0.1%)
METRORRHAGIA	1 (0.1%)	0 (0.0%)
UTERINE HAEMORRHAGE	2 (0.2%)	1 (0.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (0.2%)	2 (0.2%)
DYSPNOEA	0 (0.0%)	1 (0.1%)
PULMONARY EMBOLISM	1 (0.1%)	1 (0.1%)
PULMONARY OEDEMA	1 (0.1%)	0 (0.0%)
SURGICAL AND MEDICAL PROCEDURES	1 (0.1%)	0 (0.0%)
VAGINAL HYSTERECTOMY	1 (0.1%)	0 (0.0%)
VASCULAR DISORDERS	1 (0.1%)	1 (0.1%)
POOR VENOUS ACCESS	1 (0.1%)	0 (0.0%)
THROMBOPHLEBITIS	0 (0.0%)	1 (0.1%)

Serious "cardiac" events were imbalanced in this data pool of oral-iron controlled ("All calculated dose/first dose 1,000 mg studies"). Cardiac events in the Injectafer groups included cardiac failure (four patients, one fatal), coronary artery disease (two patients), cardiac arrest (one patient, fatal), myocardial infarction (one patient), chest pain (one patient), tachycardia (one patient) and palpitations (one patient). Three patients experienced serious cardiac events in the oral iron group and those events consisted of: cardiac failure (two patients) and myocardial ischemia (one patient).

The table below summarizes the occurrence of serious cardiac events by study.

List of all serious cardiac events by study

Populations/ Studies	Injectafer		Control	
	Age/ Gender	Cardiac SAEs	Age/ Gender	Cardiac SAEs
Post-partum anemia				
1VIT03001	28/F	Heart failure (fatal)	32/F	CHF (oral iron)
1VIT06011	39/F	Pulmonary edema with mitral valve regurgitation	No cardiac SAEs	
1VIT4002/4003	26/F	Chest pain	No cardiac SAEs	
Hemodialysis VIT-IV-CL-015	58/M	Acute anterior MI (fatal)	32/M	Ventricular arrhythemia (Venofer)
	50/F	MI		

Inflammatory bowel disease VIT-IV-CL-008	56/M	Cardiac arrest (fatal)	No cardiac SAEs	
	45/M	Tachycardia		
Non-HD CKD 1VIT04004	45/M	Worsening CAD	68/F	Demand cardiac ischemia (oral iron)
	46/M	CHF/CAD	77/F	CHF Exacerbation (oral iron)
	61/F	Palpitation		
	73/F	MI		
	54/F	CHF		

Non-fatal cardiac SAE brief narratives:

Injectafer group:

Case 1 (Study 1VIT06011- Pulmonary edema with mitral valve regurgitation):

A 38-year-old female with pre-eclampsia during pregnancy and C-section on received Injectafer 400mg on The patient's blood pressure increased to 160/90 mmHg immediately post-dose from 130/92 mmHg at pre-infusion and remained at 160/90 mmHg at 30 and 60 minutes post-dose.

On she had dyspnea and was treated with Labetolol and Lasix, and discharged home. On she was admitted to the hospital with shortness of breath and a blood pressure of 162/92 mmHg. She was diagnosed with congestive heart failure, hypertension, and 3+ mitral insufficiency with normal left ventricular function. The patient was treated with Labetolol, Lasix, and Lisinopril and was discharged on

Case 2 (Study 1VIT4002/4003- Chest pain):

A 26-year-old female with anemia secondary to heavy uterine bleeding received Injectafer 1st dose 1000 mg on and 2nd dose of 1000 mg on

On she was admitted to the hospital with chest pain which radiated down one arm. The pain resolved and she was discharged home on She refused to return to the clinic for follow-up. Records release was not signed and there is no additional follow-up on this patient. The investigator considered this event to be unrelated to study drug.

Case 3 (Study VIT-IV-CL-015- MI):

A 50-year-old female with history of hypertension and chronic kidney disease on hemodialysis received Injectafer 200 mg on and additional 5 doses of 200 mg. The last dose was .

On she had non-ST elevation MI. She was treated and recovered.

Case 4 (VIT-IV-CL-008- Tachycardia):

A 45-year-old male with inflammatory bowel disease received Injectafer 1st dose of 1000 mg on and 2nd dose of 500 mg on

On he experienced tachycardia that was recorded as a serious adverse event unrelated to the study drug. No action was taken. On he had a colitis exacerbation and anemia. On the tachycardia and anemia both resolved.

Case 5 (Study 1VIT04004- MI):

A 73-year-old female with history of chronic kidney disease and coronary artery disease received Injectafer 750 mg on

On she was admitted to hospital in respiratory arrest and was diagnosed with a myocardial infarction. The investigator considered this event to be unrelated to study drug.

Case 6 (Study 1VIT04004- CHF):

A 55-year-old female with history of chronic kidney disease and coronary artery disease with a low ejection fraction received Injectafer 1000 mg on and 500 mg on

On , she was admitted to hospital with congestive heart failure. She was treated with diuretics and recovered. The investigator considered the heart failure event to be unrelated to study drug.

Case 7 (Study 1VIT04004- CHF/CAD):

A 46-year-old male with history of chronic kidney disease, diabetes and congestive heart failure received Injectafer 1000 mg on .

On he was admitted to hospital with cough and increased lower extremity edema. He was diagnosed with congestive heart failure exacerbation and URI, and discharged on .

On he was admitted to hospital for a heart failure exacerbation again and discharged on On he had chest pain and was diagnosed as having coronary artery disease with multi-vessel stenosis. The investigator considered these events to be unrelated to study drug.

Case 8 (Study 1VIT04004- Worsening CAD):

A 45-year-old male with history of chronic kidney disease, diabetes, coronary artery disease, and a prior myocardial infarction received Injectafer 945 mg on .

On he was admitted to hospital with shortness of breath. A cardiac catheterization showed total occlusion of the right coronary artery. He was discharged on . The investigator considered this event to be unrelated to study drug.

Oral iron group:

Case 1 (Study 1VIT03001- CHF):

A 31-year-old female underwent a C-section on started ferrous sulfate 325 mg tid on .

On she developed pedal edema and was treated with a diuretic. On , she was admitted to the hospital with shortness of breath and was diagnosed with congestive heart failure. She was discharged on The investigator considered this event to be unrelated to study drug.

Case 2 (Study 1VIT04004- "Demand" cardiac ischemia):

A 66-year-old female with chronic kidney disease, myocardial infarction and congestive heart failure started ferrous sulfate 325 mg tid on

On she was admitted to the hospital with chest pain, heme-positive with Hb of 5.6 g/dL. EKG showed ST depression secondary to demand ischemia. She was transfused and given IV iron. She was discharged on The investigator considered this event to be unrelated to study drug.

Case 3 (Study 1VIT04004- Congestive Heart Failure Exacerbation):

A 77-year-old female with chronic kidney disease, diabetes, prior myocardial infarction and congestive heart failure started ferrous sulfate 325 mg three times a day on

On she was admitted to the hospital for blood transfusion and treatment for mild heart failure secondary to volume overload. She had shortness of breath for several weeks and unable to ambulate for the last 2 days. Her Hb was 5.9 g/dL. She was transfused 5 units of red blood cells and evaluated for gastrointestinal bleeding. EKG showed no ST changes. She was discharged on The investigator considered this event to be unrelated to study drug.

Venofer group:

Case 1 (Study VIT-IV-CL-015- Ventricular arrhythmia):

A 32-year-old male with hypertension, mitral incompetence, prior myocardial infarction and ventricular arrhythmia received Venofer 1st dose of 200 mg on [redacted] and additional 6 doses of 200mg. The last dose was on [redacted].

On [redacted] he experienced ventricular arrhythmia and was treated with amiodarone. The event was resolved on [redacted] The investigator considered this event to be unrelated to study drug.

Study FER-CARS-01

In FER-CARS-01 trial (Injectafer 200 mg per week) in patients with chronic heart failure, 2 cardiac SAEs (unstable angina and cardiac failure) were reported in the Injectafer group and 4 cardiac SAEs (3 cardiac failures and 1 acute MI) in the Venofer group, and 1 cardiac failure in a placebo group. As previously noted, the sample size for this study was relatively small (~ 70 patients).

5.5 Hypophosphatemia

Serum phosphate was evaluated in six studies that compared Injectafer to oral iron, including two studies in women with postpartum anemia, one study in women with heavy uterine bleeding, one cross-over safety study (7-day washout period), and two studies in non-dialysis dependent chronic kidney disease.

Mean changes in serum phosphate

The following table shows the mean changes in serum phosphate during the study in 5 controlled trials. The subsequent table shows the results for the uncontrolled trial.

Mean changes in serum phosphate

Studies	Injectafer	Oral iron	p-value
Post-partum women			
Study 1VIT03001			
Baseline	4.2 (0.58) N=174	4.2 (0.60) N=178	
Change to Day 7	-0.60 (0.69) N=169	0.0 (0.65) n=166	p<0.001
Change to Day 14	-1.1 (0.77) N=164	0.0 (0.73) n=163	p<0.001
Change to Day 28	-0.6 (0.88) N=164	0.0 (0.73) N=164	p<0.001
Change to Day 42	-0.1 (0.84) N=164	-0.1 (0.71) N=162	
Study 1VIT06011			

Baseline	4.2 (0.57) N=142	4.1 (0.58) N=147	
Change to Day 7	-0.70 (0.66) N=139	0.1 (0.53) n=147	p<0.001
Change to Day 14	-1.2 (0.76) N=139	0.1 (0.60) N=145	p<0.001
Change to Day 28	-0.6 (0.79) N=138	0.0 (0.66) N=145	p<0.001
Change to Day 42	-0.2 (0.74) N=137	0.1 (0.61`) N=143	p<0.01
Heaving Uterine Bleeding			
Study 1VIT04002/04003			
Baseline	3.7 (0.51) N=230	3.7 (0.55) N=224	
Change to minimum value	-1.9 (0.61) N=228	-0.3 (0.47) N=224	p<0.001
Change to Day 42	-1.0 (0.86) N=228	0.1 (0.56) N=224	p<0.001
Non-dialysis dependent CKD			
Study 1VIT04004			
Baseline	4.4 (0.89) N=147	4.4 (0.82) N=103	
Change to Day 14	-0.6 (0.79) N=145	0.1 (0.66) n=98	p<0.001
Change to Day 28	-0.5 (0.90) N=140	0.1 (0.81) N=87	p<0.001
Change to Day 42	0.2 (0.78) N=5	1.2 (0.84) N=2	
Change to Day 56	-0.2 (0.96) N=135	-0.2 (0.77) N=85	
Study 1VIT05006 Cross-over study	**Injectafer**	**placebo**	
Baseline	4.0 (0.94) N=593	4.0 (0.94) N=593	
Change to Day 7	-1.1 (0.81) N=551	-0.5 N=551	p<0.001

The following table shows the mean changes in serum phosphate during the study in Study 1VIT05005, an uncontrolled trial.

Mean changes in serum phosphate

Study 1VIT05005	Injectafer
Baseline	4.31 (0.86) N=127
Change to Day 28	-0.32 (1.0)

	N=117
Change to Day 56	-0.21 (0.98) N=109
Change to Day 84	-0.23 (1.03) N=105
Change to Day 112	-0.18 (1.18) N=97
Change to Day 140	-0.20 (0.96) N=94
Change to Day 168	-0.17 (1.01) N=77
Change to Day 196	-0.16 (1.08) N=70
Change to Day 224	-0.28 (1.11) N=56
Change to Day 255	-0.19 (1.07) N=50
Change to Day 280	-0.21 (0.98) N=70
Change to Day 308	-0.13 (0.67) N=56

Serum Phosphate <2.0 mg/dL

The incidence of serum phosphate < 2.0 mg/dL was relatively high among patients receiving Injectafer, ranging from 3.8% to 70.1% of Injectafer-treated patients in the clinical studies as compared to 0% in oral-iron-treated patients (See table below).

Serum Phosphate < 2.0 mg/dL

Studies	**Injectafer**	**Oral iron**
Post-partum		
1VIT03001	14/174 (8.0%)	0/178 (0%)
1VIT06011	12/142 (8.5%)	0/147 (0%)
Heavy uterine bleeding		
1VIT04002/1VIT04003	157/224 (70.1%)	0/219 (0%)
Cross-over safety study		
1VIT05006	81/505 (16.0%)	48/487 (9.9%) placebo
Non-hemodialysis dependent CKD		
1VIT04004	4/105 (3.8%)	0/75 (0%)
1VIT05005	7/98 (7.1%)	-

The following table shows the lowest available serum phosphate value in these studies. One subject had serum phosphate <1.0 mg/dL: 0.9 mg/dL.

Studies	Serum phosphate lowest available value (mg/dL)		
	1.5-1.9	1.0-1.4	<1.0
Post-partum			
1VIT03001 (n=174)	13 (7.5%)	1 (0.6%)	0
1VIT06011 (n=142)	11 (7.7%)	1 (0.7%)	0
Heavy uterine bleeding			
1VIT04002/1VIT04003 (n=224)	113 (50.4%)	43 (19.2%)	1 (0.4%)
Non-hemodialysis dependent CKD			
1VIT04004 (n=105)	4/105 (3.8%)	0 (0%)	0
1VIT05005 (n=98)	5/98 (5.1%)	2 (2.0)	0

5.6 Hypersensitivity Reactions

Three hypersensitivity reactions were reported among Injectafer-treated patients (all non-serious) and one was reported in an oral-iron-treated patients.

In the Injectafer-treated patients, one hypersensitivity reaction was reported in Study VIT-IV-CL-008, another was reported in Study VIT-IV-CL-009, and another was reported in Study FER-CARS-01. These are summarized below:

a. One event was mild in intensity and considered possibly related to study medication by the investigator. The event occurred on the same day as first study dose of medication administration.

b. The second event occurred one day after the second infusion. The subject developed symptoms of allergy that were considered as severe by the investigator but not further specified. The event was considered "certainly related" to study drug by the investigator and resolved without sequelae within 5 days.

c. The hypersensitivity event reported in Study FER-CARS-01 was mild in intensity and considered related to study medication. The event occurred 1 day after the subject's 6th dose of study medication (200 mg of Injectafer). Study medication was temporarily discontinued and the event resolved 27 days later. Study medication was resumed 14 days after the event resolved with no subsequent adverse events.

Other adverse events indicative hypersensitivity/allergic reactions are listed in the table below.

Adverse events indicative hypersensitivity/allergic reactions

SOC Preferred Term					Crossover Study	
	FCM (N=1414)	Oral Iron (N=834)	Venofer (N=145)	Placebo (N=15)	FCM (N=584)	Placebo (N=569)
At Least 1 Adverse Event	55 (3.9%)	16 (1.9%)	3 (2.1%)	0	16 (2.7%)	8 (1.4%)
Bronchospasm	0	1 (0.1%)	0	0	0	0
Eye pruritus	1 (0.1%)	0	0	0	0	0
Eyelids pruritus	0	0	0	0	0	1 (0.2%)
Face oedema	0	0	0	0	1 (0.2%)	0
Genital pruritus female	1 (0.1%)	0	0	0	0	0
Idiopathic urticaria	1 (0.1%)	0	0	0	0	0
Infusion site pruritus	1 (0.1%)	0	0	0	0	0
Infusion site rash	0	0	0	0	2 (0.3%)	0
Injection site urticaria	0	0	0	0	1 (0.2%)	0
Pruritus	12 (0.8%)	2 (0.2%)	3 (2.1%)	0	3 (0.5%)	1 (0.2%)
Pruritus ani	0	0	0	0	1 (0.2%)	0
Pruritus generalized	0	1 (0.1%)	0	0	3 (0.5%)	2 (0.4%)
Pruritus genital	1 (0.1%)	0	0	0	0	0
Rash	23 (1.6%)	10 (1.2%)	1 (0.7%)	0	6 (1.0%)	2 (0.4%)
Rash erythematous	3 (0.2%)	0	0	0	2 (0.3%)	0
Rash generalized	0	0	0	0	2 (0.3%)	0
Rash macular	3 (0.2%)	0	0	0	0	0
Rash maculopapular	1 (0.1%)	0	0	0	0	0
Rash papular	0	0	0	0	0	1 (0.2%)
Rash pruritic	2 (0.1%)	1 (0.1%)	0	0	1 (0.2%)	0
Swelling face	0	0	0	0	0	1 (0.2%)
Urticaria	11 (0.8%)	3 (0.4%)	0	0	0	0
Urticaria generalized	1 (0.1%)	0	0	0	0	0
Wheezing	1 (0.1%)	0	0	0	0	0

All Multicenter Studies: GI: VIT-IV-CL-003 and VIT-IV-CL-008; Postpartum: VIT-IV-CL-009, 1VIT03001, and 1VIT06011; HUB: 1VIT04002/1VIT04003; HD: VIT-IV-CL-015 and VIT-53214; NDD-CKD: 1VIT04004; IDA: 1VIT05006; CHF: FER-CARS-01.

5.7 Adverse events leading to premature discontinuation of subjects from a study or to discontinuation of the study drug

In the active-controlled studies, the overall incidence of treatment-emergent adverse events resulting in discontinuation of a subject from a study was 1.3% in the Injectafer group, 1.8% in the oral iron group, and 4.1% in the Venofer group, as shown below

Adverse events leading to premature discontinuation of participation in a study (experienced by ≥ 2 subjects in any group in active-controlled multicenter studies)

SOC Preferred Term	FCM (N=1206)	Oral Iron (N=834)	Venofer (N=145)	Placebo (N=15)
At Least 1 Adverse Event	16 (1.3%)	15 (1.8%)	6 (4.1%)	0
Cardiac disorders	5 (0.4%)	0	1 (0.7%)	0
Myocardial infarction	2 (0.2%)	0	0	0
Gastrointestinal disorders	2 (0.2%)	14 (1.7%)	3 (2.1%)	0
Abdominal pain upper	0	2 (0.2%)	0	0
Colitis ulcerative	1 (0.1%)	2 (0.2%)	0	0
Diarrhoea	0	5 (0.6%)	0	0
Gastrointestinal haemorrhage	0	0	2 (1.4%)	0
Melaena	0	0	2 (1.4%)	0
Nausea	0	5 (0.6%)	0	0
Vomiting	0	3 (0.4%)	0	0
General disorders and administration site conditions	5 (0.4%)	1 (0.1%)	0	0
Infusion site reaction	2 (0.2%)	0	0	0
Infections and infestations	4 (0.3%)	3 (0.4%)	1 (0.7%)	0
Sepsis	2 (0.2%)	0	0	0
Nervous system disorders	0	3 (0.4%)	2 (1.4%)	0
Dizziness	0	2 (0.2%)	0	0
Headache	0	1 (0.1%)	2 (1.4%)	0
Skin and subcutaneous tissue disorders	3 (0.2%)	0	0	0
Rash	2 (0.2%)	0	0	0
Vascular disorders	0	1 (0.1%)	4 (2.8%)	0
Hypotension	0	0	2 (1.4%)	0

All Active-Controlled Multicenter Studies: GI: VIT-IV-CL-008; Postpartum: VIT-IV-CL-009, 1VIT03001, and 1VIT06011; HUB: 1VIT04002/1VIT04003; HD: VIT-IV-CL-015; NDD-CKD: 1VIT04004; CHF: FER-CARS-01.

In the active-controlled, multi-center studies, the overall incidence of adverse events resulting in premature discontinuation of the study drug was 1.6% in the Injectafer group, 3.0% in the oral iron group and 2.1% in the Venofer group as shown below.

Adverse events resulting in premature discontinuation of the study drug (experienced by ≥ 2 subjects in any group in active-controlled multicenter studies)

SOC Preferred Term	FCM (N=1206)	Oral Iron (N=834)	Venofer (N=145)	Placebo (N=15)
At Least 1 Adverse Event	19 (1.6%)	25 (3.0%)	3 (2.1%)	0
Gastrointestinal disorders	1 (0.1%)	20 (2.4%)	2 (1.4%)	0
Abdominal pain upper	0	2 (0.2%)	0	0
Colitis ulcerative	0	2 (0.2%)	0	0
Constipation	0	2 (0.2%)	0	0
Diarrhoea	0	5 (0.6%)	0	0
Gastrointestinal haemorrhage	0	2 (0.2%)	2 (1.4%)	0
Melaena	0	0	2 (1.4%)	0
Nausea	0	7 (0.8%)	0	0
Vomiting	0	3 (0.4%)	0	0
General disorders and administration site conditions	6 (0.5%)	1 (0.1%)	0	0
Infusion site reaction	2 (0.2%)	0	0	0
Nervous system disorders	0	3 (0.4%)	0	0
Dizziness	0	3 (0.4%)	0	0
Skin and subcutaneous tissue disorders	8 (0.7%)	0	0	0
Rash	4 (0.3%)	0	0	0
Urticaria	2 (0.2%)	0	0	0

All Active-Controlled Multicenter Studies: GI: VIT-IV-CL-008; Postpartum: VIT-IV-CL-009, 1VIT03001, and 1VIT06011; HUB: 1VIT04002/1VIT04003; HD: VIT-IV-CL-015; NDD-CKD: 1VIT04004; CHF: FER-CARS-01.

5.8 Common Adverse Events

In all multicenter studies, at least 1 adverse event was experienced by 49% of subjects in the Injectafer group, 53% of subjects in the oral iron group and 40% of subjects in the Venofer group.

As previously noted, the data may be analyzed using multiple types of data "pooling." Some of these approaches are summarized below with emphasis upon the " All calculated dose/first dose 1,000 mg studies " dose regimen as the approach most applicable to assessing the safety.

"All calculated dose/first dose 1,000 mg dose regimen studies"

In oral-iron controlled trials (all calculated dose/first dose 1,000 mg studies), at least 1 treatment-emergent adverse event was experienced by 48.2% of subjects in the Injectafer group and 53.1% of subjects in the oral iron group ($p = 0.03$).

In the Injectafer group, the most frequently experienced adverse event was headache (8.3%), abdominal pain (2.6%), blood phosphate decreased (2.5%), nausea (2.2%), dizziness (2.2%), rashes (2.1%), and nasopharyngitis (2.1%).

In the oral iron group, the most frequently experienced adverse events were constipation (12.6%), headache (7.7%), nausea (7.4%), diarrhea (4.0%), nasopharyngitis (2.9%), vomiting (2.5%), and dizziness (2.0%).

Patients in the oral iron group frequently reported gastrointestinal disorders (31%), primarily constipation (12.6%). Adverse events reported more in the Injectafer group as compared to oral iron included cardiac disorders, abdominal pain, fatigue, peripheral edema, pyrexia, influenza, serum phosphate decreased, arthralgia, back pain, myalgia, dizziness, dysgeusia, headache, and rash.

Adverse events (≥ 2.0% in either group) among "all calculated dose/first dose 1,000 mg studies " studies

SOC Preferred Term	FCM (N=1057)	Oral Iron (N=834)	p-value
At Least 1 Adverse Event	509 (48.2%)	443 (53.1%)	0.0332
Gastrointestinal disorders	141 (13.3%)	260 (31.2%)	<0.0001
Abdominal pain	28 (2.6%)	16 (1.9%)	
Constipation	20 (1.9%)	105 (12.6%)	
Diarrhoea	16 (1.5%)	33 (4.0%)	
Nausea	23 (2.2%)	62 (7.4%)	
Vomiting	10 (0.9%)	21 (2.5%)	
Infections and infestations	144 (13.6%)	103 (12.4%)	0.4498
Nasopharyngitis	22 (2.1%)	24 (2.9%)	
Investigations	74 (7.0%)	31 (3.7%)	0.0023
Blood phosphate decreased	26 (2.5%)	0	
Nervous system disorders	125 (11.8%)	92 (11.0%)	0.6115
Dizziness	23 (2.2%)	17 (2.0%)	
Headache	88 (8.3%)	64 (7.7%)	
Skin and subcutaneous tissue disorders	70 (6.6%)	20 (2.4%)	<0.0001
Rash	22 (2.1%)	10 (1.2%)	

All Calculated Dose/First-Dose 1,000 mg Studies: GI: VIT-IV-CL-008; Postpartum: VIT-IV-CL-009, 1VIT03001, and 1VIT06011; HUB: 1VIT04002/1VIT04003; NDD-CKD: 1VIT04004

6. OVERALL ASSESSMENT

6.1 Efficacy

For the currently proposed indication for treatment of iron deficiency anemia in patients with heavy uterine bleeding and in post-partum anemia, efficacy results from two studies showed superiority of Injectafer to oral iron and two studies showed non-inferiority to oral iron product in treatment of iron deficiency anemia. These data support the efficacy of Injectafer to replenish iron stores and treat iron deficiency anemia. The major outcomes related to increases in hemoglobin concentrations.

6.2 Safety

Mortality

Safety results raised significant safety concerns due to a safety signal for a mortality risk associated with Injectafer. There were 10 deaths in Injectafer-treated patients as compared to one death in the control patients in all completed clinical trials (0.48% vs. 0.06%). Five of the six deaths among Injectafer-treated patients in randomized trials occurred in studies using the proposed first-dose 1000 mg dose regimen.

The assessment of the mortality safety signal is not based solely upon the numeric imbalance in deaths. Instead, the overall pattern of safety findings contributes to the signal, as evidenced by an imbalance in serious adverse event rates and "cardiac" serious adverse event rates (compared to oral iron) and a relatively high rate of clinically notable hypophosphatemia. Some publications have suggested that hypophosphatemia may

contribute to cardiac dysfunction. Overall, the totality of the information raises important concerns for Injectafer safety, especially for the proposed market population of women and the treatment alternatives (including oral iron).

Clinical Pharmacology Summary

Background of Iron Storage and Metabolism:

Body iron content is usually described as 3 - 4 g, of which 60% in found in hemoglobin. The blood protein transferrin transports iron from the gut to cells. Serum ferritin is an iron-storage protein that is commonly regarded as a measure of total body iron content. Healthy male serum ferritin levels generally range from 12-300 ng/mL and 12-150 ng/mL for female. Serum iron measurements generally refer to transferrin-bound iron. Total iron binding capacity (TIBC) is the concentration of iron necessary to saturate iron-binding sites of transferrin. Normal transferrin saturation is approximately 20-30%. Unsaturated iron-binding capacity (UIBC) is the difference between TIBC and serum iron.

Drug:

Injectafer (VIT-45) is a polynuclear iron (III)-hydroxide complex with a molecular weight of 15,000 Dalton. The drug product is a dark brown, non transparent, aqueous solution. The product contains no pharmacological activity other than its ability to deliver utilizable iron to iron storage and transport proteins in the body (ferritin and transferrin).

Summary of Pharamcokinetic (PK) Studies:

Four clinical pharmacology studies were conducted in support of this NDA.
A dose escalation PK Study (VIT-IV-CL-02) in patients with mild iron deficiency anemia was performed to study safety and tolerability of the drug. The study included single IV doses of 100, 500, 800, and 1000 mg via a bolus IV injection or IV infusion. The increase in Cmax for total serum iron concentration did not increase linearly with dose (particularly in 800 mg dose group). The average terminal half-life ($t_{1/2}$) of Injectafer (injected or infused) ranged from 10.3 h to 17.7 hours.

The intravenously injected iron complex Injectafer 100 mg led to a maximum total serum iron of 37 µg/mL (geometric mean Cmax). A short infusion of Injectafer at doses of 500, 800, 1000 mg led to mean maximum total serum iron concentrations of 156, 319 and 331 µg/mL, respectively. Particularly, the 800 mg dose deviated from the dose-linear increase, while the maximum level after 1000 mg Injectafer was approximately doubled when compared to the 500-mg dose. Similarly, average AUC was 426 µg-h/mL for 100 mg Injectafer. The increase in AUC values with incremental dose of Injectafer was higher than expected for dose-proportional increases; the geometric means for 500, 800 and 1000 mg doses were 2443, 5218, 6311 µg-h/mL, respectively. The Tmax was about 30 minutes for the lower doses (100 and 500 mg). However, increasing Injectafer doses led to a shift of Tmax that was about 1 h or longer at 800 to 1000 mg Injectafer. The geometric mean residence time (MRT) was less than a day (16.9 h to 23.6 h). The total body clearance, CL, was low and averaged at approximately 3.4 mL/min for the 100- and 500-mg doses and at approximately 2.6 mL/min for the two higher doses. The majority of

administered iron complex was utilized or excreted within 24 h after a low dose of 100 mg and within 72 h after higher doses of 500-1000 mg.

Pharmacodynamic Parameters:

The pharmacodynamic variables evaluated included the measurement of serum iron concentrations, serum ferritin, total iron binding capacity and transferrin saturation (TfS). In addition, the hemoglobin levels and reticulocyte counts were also measured. The percent increase in transferrin saturation for 500, 800, 1000 mg was 76, 63, 71%, respectively at 24-36 hrs post-dose (Table I). Iron binding capacity was fully utilized (as shown by 90% transferrin saturation) after doses of 500, 800 and 1000 mg. Unsaturated iron binding capacity (UIBC) is reciprocally linked with the post-dose transferrin saturation. As expected, no major change was observed following placebo administration. In contrast, the IV administration of Injectafer led to steep decline in UIBC, particularly in 500- 800- and 1000 mg VIT-45 dose groups. However, no major notable differences were seen in different higher dose groups (500, 800, and 1000 mg) (Figure 1).

A dose optimization and a justification of dose based on pharmaco-dynamic variables have not been provided by the sponsor.

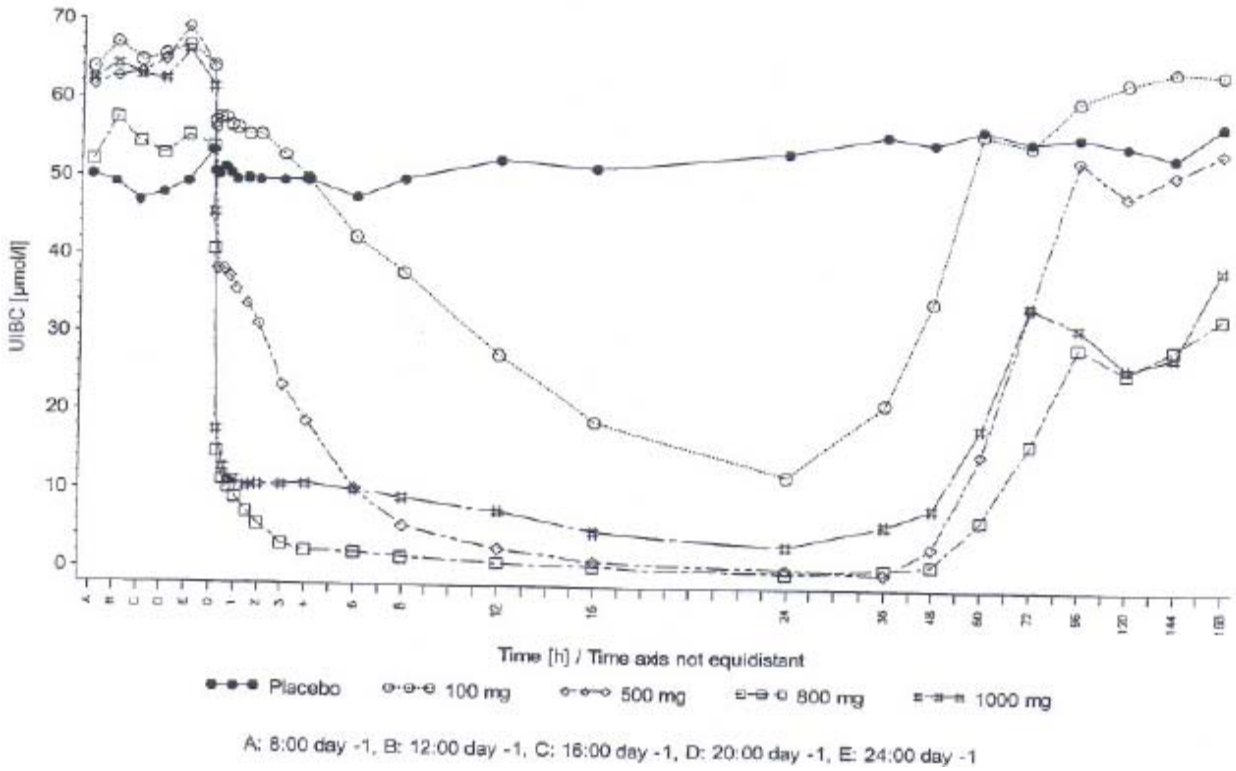

Figure 1. Mean Unsaturated Iron Binding Capacity [µmol/L] for different doses and placebo

The increase in serum ferritin concentration was dose dependent but not dose-linear. Maximum serum ferritin concentrations after dosing and the respective pre-dose concentrations are summarized in Table II. The mean serum ferritin concentration on Day -1 (measured at 08:00, 12:00, 16:00, 20:00 and 24:00 hours) were approximately 2 to 6 ng/mL across the different treatment groups. After dosing with placebo, the mean ferritin levels remained unchanged about 5ng/mL until 168 – hour assessment. In contrast, ferritin levels started to rise approximately 6 to 12 hours after dosing in all actively treated patient groups. The highest serum concentrations were reached between 48 hours (100 mg Injectafer) and 120 hours (800 and 1000 mg Injectafer) after dosing, with a 23- to 210 fold increase above baseline. The increase in serum ferritin concentrations was dose dependent, but not strictly linear.

Table I. Maximum mean % changes in transferrin saturation for various doses of Injectafer

Dose	100 mg	500 mg	800 mg	1000 mg
Change	+63(±22)	+76(±8)	+63(±5)	+71(±12)

Table II. Serum Ferritin Concentrations after administration of different doses of Injectafer (VIT-45)

Serum ferritin	Statistics	Treatment / Iron as VIT-45 (mg)				
		Placebo	100	500	800	1,000
Serum ferritin, pre-dose concentration (ng/mL)	Mean (SD)	5.8 (6.0)	2.1 (1.5)	5.2 (6.6)	4.0 (2.5)	3.1 (2.0)
Serum ferritin, max. concentration (ng/mL)	Mean (SD)	6.8 (4.4)	48.5 (20.0)	423 (400)	488 (165)	652 (218)
Time of peak (h)	-	24	48	96	120	120

Conclusion:

Based upon three pharmacodynamic parameters a) mean changes in transferrin saturation, b) unsaturated iron binding capacity and c) the serum ferritin concentrations, one readily concludes that a lower Injectafer dose may adequately supply bone marrow iron and potentially lessen the risk for adverse events.

A high serum ferritin concentration has been hypothesized (in some publications) to be related to oxidative stress and cardiovascular disease. The serum ferritin concentrations

increased from 2-5 ng/mL (predose levels) to 420-650 ng/mL for subjects given various doses of Injectafer. Serum ferritin concentrations for normal male are 12-300 ng/mL and 12-150 ng/mL for female. The extent to which the increases in serum ferritin associated with the proposed Injectafer dose regimen may have contributed to adverse events is unclear.

BIOMETRICS REVIEW

Date: December 6, 2007

To: Dwaine Rieves, M.D., Acting Division Director
Division of Medical Imaging and Hematology Products

Min Lu, M.D., M.P.H., Medical Officer
Division of Medical Imaging and Hematology Products

Through: George Rochester, Ph.D., R.A.C., Lead Mathematical Statistician
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From: Yu-te Wu, Ph.D., M.P.H., Mathematical Statistician
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Drug: Ferinject® (iron carboxymaltose injection)

NDA: 22-054/Amendment No. 047

Indications: Treatment of iron deficiency anemia in patients with

- Heavy uterine bleeding
- Post-partum anemia
- Inflammatory bowel disease
- Hemodialysis
- Non-hemodialysis chronic kidney disease.

Subject: Statistical review of the mortality risk in the entire clinical program as presented in the sponsor's re-analysis of mortality risk submitted on September 12, 2007, amendment No. 047. The Quantitative Safety and Pharmacoepidemiology Group was consulted to evaluate the sponsor's re-analysis of possible association of the use of the drug and the risk of mortality.

1. Summary

The purpose of this review is to assess the effect of ferric carboxymaltose on mortality risk in the entire clinical program. Ferric carboxymaltose is an injectable iron product developed for the treatment of iron deficiency anemia in patients with heavy uterine bleeding, post-partum anemia, inflammatory bowel disease, hemodialysis and non-hemodialysis chronic kidney disease. In the clinical program, ferric carboxymaltose was investigated in fourteen small studies in different study populations. Overall, there was an imbalance in mortality with 10 deaths (from any causes) in the ferric carboxymaltose-treated group as compared to 1 death in the combined-control group based on controlled and uncontrolled studies. Limiting the analysis to the controlled studies, the numerical imbalance remained with 6 deaths in the ferric carboxymaltose-treated group versus 1 death in the control-treated group.

The stratified analysis on the pooled dataset of nine controlled studies suggests that the mortality risk was numerically greater in the ferric carboxymaltose-treated group compared to the control-treated group with point estimate of odds ratio > 1 and risk difference > 0, but the difference did not reach the 0.05 significance level. Different statistical approaches were applied to assess the risk and the resulting conclusions were similar.

The safety signal of increased mortality risk associated with ferric carboxymaltose cannot be ruled out, even though the difference did not reach statistical significance. The controlled studies were limited in size [72-594] and were not adequately powered to detect the differential mortality risk between ferric carboxymaltose and control groups. Additional safety data from further studies are needed in order to better quantify the mortality risk.

2. Background

Ferinject® (ferric carboxymaltose) is an injectable iron product being developed for treatment of iron deficiency anemia in patients with heavy uterine bleeding, post-partum anemia, inflammatory bowel disease, hemodialysis and non-hemodialysis chronic kidney disease (non-HD CKD). The NDA was submitted in June, 2006 and received a non-approvable response in July, 2007. The Not Approvable letter indicated the proposed Ferinject dose regimen is accompanied with an unacceptable risk for death, serious adverse reactions and clinically important hypophosphatemia. Eleven completed clinical studies and two ongoing studies were included in the analyses. A total of 1851 patients in completed clinical trials and additional 198 patients in two ongoing trials were exposed to ferric carboxymaltose treatment. A total of 1527 patients received the control treatments including 832 patients who received oral iron product, 118 patients who received Venofer and 577 who received placebo. The summary of the mortality data in completed and ongoing trials included in the integrated review of safety by the medical reviewer, Dr. Lu, is listed in Appendix I.

Below is the summary of findings from an analysis conducted by the medical reviewer, Dr. Lu. Ten deaths were reported among subjects exposed to ferric carboxymaltose while no deaths were reported among subjects exposed to the comparator. The mortality rate was significantly higher in ferric carboxymaltose-treated

patients as compared to that in the control-treated patients (ferric carboxymaltose vs. control: 0.49% (10/2049) vs. 0% (0/1527), p=0.0067 using Fisher's exact test calculated by this statistical reviewer, and the results were the same as stated in the statistical review by Dr. Misra). Most of the reported deaths occurred within 30 days of the last dose administration. Six of these deaths were reported from controlled studies. When limiting the analyses to controlled studies, the mortality difference remained significantly higher in the ferric carboxymaltose-treated patients as compared to control-treated patients (ferric carboxymaltose vs. control: 0.34% (6/1784) vs. 0% (0/1527), p=0.034 using Fisher's exact test calculated by this statistical reviewer, and the results were the same as stated in the statistical review by Dr. Misra).

The sponsor submitted amendment #047 in September 2007 in response to the Not Approvable letter. The sponsor did not agree with the FDA's analysis of mortality risk and stated that "One death occurred in the comparator arm in the Congestive Heart Failure/Chronic Kidney disease study (FER-CARS-01)" which was not included in the FDA's analysis. The sponsor's Integrated Summary of Safety and Statistical Position Paper were revised to reflect the incorporation of studies not included previously. The Quantitative Safety and Pharmacoepidemiology Group within the Office of Biostatistics was consulted to evaluate the sponsor's re-analysis of morality risk.

2.1 Objective

The objective of this review is to examine the mortality data available in the clinical development program and to provide overall mortality risk assessment using the data provided in the sponsor's re-analysis document submitted to FDA in September 12, 2007.

3. Statistical methods

3.1 Analysis population

The primary analysis population is the safety population in nine completed and controlled clinical studies, including the cross-over study and the Congestive Heart Failure/Chronic Kidney disease study (FER-CARS-01). The cross-over study was included as a controlled study because patients had the opportunity to receive either ferric carboxymaltose or placebo, the follow-up duration was comparable in two treatment arms, and also this study was comprised of about 21 percent of entire exposed population. Two PK studies were not included in the analysis due to their small sizes.

Analysis was also conducted for the patient population in eight randomized controlled studies, excluding the cross-over study; and also in three uncontrolled studies. Table 1 gives a brief summary of the studies included in the review.

Table 1: Summary of clinical studies included in the review

Study population	Study design	Ferinject carboxymaltose Dose regimen	Treatment group	
			Ferinject # of patients	Control # of patients
Controlled studies				
Post-partum anemia				
1VIT03001	Open-label, R, MC, multiple-dose, AC	Max. dose – 1000mg, Max cumulative dose – 2500 mg	174	178
VIT-IV-CL-009			227	117
1VIT06011			142	147
Heavy uterine bleeding				
1VIT04002/04003	Open-label, R, MC, multiple-dose, AC	Same as above	230	226
Inflammatory bowl dz				
VIT-IV-CL-008	Open-label, R, MC, multiple-dose, AC	Same as above	137	63
Hemodialysis				
VIT-IV-CL-015	Open-label, R, MC, multiple-dose, AC	200 mg, 2 or 3 times/weekly, max. cumulative dose – 2500 mg	119	118
Iron deficiency anemia				
1VIT05006	Single-dose, cross-over	15 mg/kg Max dose – 1000 mg	584	569
Non-HD CKD				
1VIT04004	Open-label, R, MC, AC	Max dose – 1000 mg Max cumulative dose – 2500 mg	147	103
CHF, renal failure, iron deficiency				
FER-CARS-01	R, double-blind. MC, parallel group	200 mg, Max cumulative dose – Ganzoni formula (varied by individual)	30	42
Uncontrolled studies				
Inflammatory bowl dz				
VIT-IV-CL-003	Open-label, MC, multiple-dose,	Max cumulative dose – 2000 mg	46	0
Hemodialysis				
VIT-53214	Open-label, MC, multiple-dose	200 mg, 2 or 3 times/weekly, max. cumulative dose – 2500 mg	162	0
Non-HD CKD				
1VIT05005	Long-term extension of 1VIT04004	Max dose – 1000 mg	127	0

R: Randomized, AC: Active-controlled, MC: Multi-center
Control group includes patients taking oral iron, Venofer and placebo

3.2 Analytic methods

The primary analysis was to compare the mortality risk between ferric carboxymaltose and control (combined oral iron, Venofer and placebo groups) groups in the primary analysis population (i.e., nine controlled studies including cross-over study). The estimate of the odds ratio was chosen to be the primary measure as the outcome was considered a short-term response (most deaths occurred within 30 days following the last dose of study drug) and treatment groups (within each controlled studies) had comparable follow-up mechanisms. The adjusted odds ratio and 95% confidence interval were calculated with stratification by the individual trials using the exact method[1], the Mantel-Haenzel method without continuity correction[2-4] and Peto one-step method[5] as described by Bradburn et. al[6] for the rare event situation. A stratified estimate allows the event rates to vary from study to study, therefore controlling for the between-study variation from different study designs (including patient population, study duration, treatment regimen and study size). Heterogeneity among studies was tested by Zelen's exact test.

The exact method[1] estimates the odds ratio on the basis of evaluating all possible permutations of a conditional hypergeometric response, and is an extension of Fisher's exact test which allows for separate probabilities within each stratum. The Mantel-Haenzel test[2-4] uses the pooled variance estimator, proposed by Robins, Breslow and Greenland (RBG variance, 1986), to compute the Wald z-test method for the hypothesis test and 95% confidence limits. The Peto one-step method[5] computes an approximation of the log-odds from the ratio of the efficient score to the Fisher information, both evaluated under the null hypothesis. These quantities are estimated by the sum of the differences between the observed and expected numbers of events in the treatment arms and by the sum of the conditional hypergeometric variances. The Peto method also uses the Wald z-test method for the hypothesis test. The main limitation of these approaches is that trials with no events in both treatment groups are excluded from the analysis.

The adjusted analysis of risk difference based on the Mantel-Haenszel approach[7] was also performed to make use of trials with no events in both treatment groups. This secondary analysis was conducted to examine the effect of trials without events.

In addition to the analysis on the pooled dataset, the odds ratio (OR, 95% confidence interval) and risk difference (RD, 95% confidence interval)[7] were calculated for each of the controlled studies using the exact method. The odds ratio is not estimable for those trials with no events in both treatment groups, whereas the risk difference method is able to provide an estimate for each trial.

The same analytic approaches were applied to the pooled dataset of eight controlled studies, excluding the cross-over study. The mortality data from the three uncontrolled studies were summarized separately using descriptive statistics; stratified analysis was not applicable for these types of studies due to lack of a comparator group.

4. Results

There were no notable differences in demographics and baseline characteristics between treatment groups within controlled studies. In nine completed controlled clinical

studies, six deaths occurred among ferric carboxymaltose-treated subjects (one of them was from the cross-over study) and one death occurred among Venofer-treated subjects. Five deaths were observed within 15 days of the last dose of study drug and one death happened at day 35 after the last dose of study drug. Table 2 shows the percent of mortality, estimates of odds ratio (95% CI) and risk difference (95% CI) for individual studies and the results of pooled analysis stratified by study. At the study-level, due to zero count in one of the treatment arms, the odds ratio estimates were either zero or infinity. The risk difference is a more applicable measure in this case. Among six controlled studies with deaths occurring in either arm, five out of six studies show a mortality risk in the ferric carboxymaltose-treated group greater than that in the control-treated group with risk difference > 0. The exception was the FER-CARS-01 study where one death occurred in the Venofer group resulting in an estimate of risk difference of -2.38%. In the primary analysis population (all controlled studies, including the cross-over study), the crude mortality rate is 0.335% in the ferric carboxymaltose group vs. 0.064% in the control group. Results from stratified analysis suggest that the mortality risk was numerically greater in the ferric carboxymaltose-treated group compared to the control-treated group with OR > 1 and RD > 0, but the differences did not reach the 0.05 significance level, with 95% CI of ORs including 1 and 95% CI of RD including 0; and the conclusions were similar using different analytic approaches. For the pooled analysis on 8 controlled studies (excluding the cross-over study), results were similar suggesting that the mortality risk was numerically greater in the ferric carboxymaltose-treated group compared to the control-treated group, although the difference did not reach the significance level.

Table 2: Odds ratio (95% CI), risk difference (95% CI) by study and pooled analysis adjusting the study factor

Study population	Treatment group: Ferinject # of deaths/# of subjects (%)	Treatment group: Control # of deaths/# of subjects (%)	Odds Ratio (95% CI)[1]	Risk diff (%) (95% CI)[2] w/o adjust
Post-partum anemia				
1VIT03001	1/174(0.57%)	0/178	∞ (0.0538, ∞)	0.57(-1.64,3.45)
VIT-IV-CL-009	0/227	0/117	--	0(-3.42,1.70)
1VIT06011	0/142	0/147	--	0(-2.64,2.82)
Heavy uterine bleeding				
1VIT04002/04003	0/230	0/226	--	0(-1.77, 1.72)
Inflammatory bowl dz				
VIT-IV-CL-008	1/137(0.73%)	0/63	∞ (0.0242, ∞)	0.73(-5.37,4.05)
Hemodialysis				
VIT-IV-CL-015	1/119(0.84%)	0/118	∞ (0.0522, ∞)	0.84(-2.52,5.06)
Iron deficiency anemia				
1VIT05006 (cross-over)	1/584(0.17%)	0/569	∞ (0.0513, ∞)	0.17(-0.54,1.03)
Non-HD CKD				
1VIT04004	2/147(1.36%)	0/103	∞ (0.2019, ∞)	1.36(-2.6,4.98)
CHF, renal failure and iron deficiency				
FER-CARS-01	0/30	1/42(2.38%)	0 (0,26.60)	-2.38(-12.7,10.15)
Total	6/1790(0.335%)	1/1563(0.064%)		
Pooled analysis				
Primary Analysis – all controlled studies including cross-over study				
Exact method			5.29(0.76,124.2)	--
Mantel-Haenzel OR without continuity adjustment			6.33(0.64,62.49)	0.27(-0.0067,0.548)
Peto OR			3.71(0.82,16.8)	--
Sensitivity analysis 1– all controlled studies, excluding cross-over study				
Exact method			4.32(0.58,104.7)	--
Mantel-Haenzel OR without continuity adjustment			5.14(0.50,53.1)	0.32(-0.063,0.71)
Peto OR			3.31(0.65,16.9)	--

[1] Odds ratio and confidence interval were estimated by exact method.
[2] Agresti and Min (2001)

Table 3 shows the mortality rate in three uncontrolled studies. Four deaths occurred among ferric carboxymaltose-treated patients. Two deaths from hemodialysis study happened within 20 days after the last dose of study drug and the other deaths from non-dialysis CKD study happened at days 46 and 98 after the last dose of study drug. Due to the lack of the comparator group, data from these uncontrolled studies cannot be combined with the primary analysis set for the adjusted analyses. Crude (unadjusted) analysis is not very appropriate given that the studies varied widely in terms of study design, dose regimen, treatment duration and study population.

Table 3: Mortality risk in the uncontrolled studies

Study population	Treatment group
	Ferinject # of deaths/# of subjects (%)
Inflammatory bowel dz	
VIT-IV-CL-003	0/46(0%)
Hemodialysis	
VIT-53214	2/162(1.23%)
Non-HD CKD	
1VIT05005	2/127(1.57%)

5. Conclusions and Discussions

The analysis on the pooled dataset of nine controlled studies suggests that the mortality risk was numerically greater in the ferric carboxymaltose-treated group compared to control-treated group with point estimate of OR > 1 or RD > 0, irrespective of different analytic approaches. Even though the test results did not reach the 0.05 significance level, the safety signal of mortality risk associated with the ferric carboxymaltose therapy cannot be ruled out for the following reasons:

1) From nine controlled studies, six deaths occurred in the ferric carboxymaltose group whereas only one death occurred in the control group
2) The point estimates of the odds ratios and risk differences from the stratified analyses all suggest that ferric carboxymaltose was associated with a greater mortality risk than the control group
3) The size of the controlled studies was not adequately powered to detect the differential mortality risk between ferric carboxymaltose and control groups

The exact, Mantel-Haenszel without zero-cell correction and Peto methods are recommended in the statistical literature for the rare event situation. Each method has advantages and disadvantages depending on the underlying event rate, the likely size of treatment effect, and the balance in the numbers of treated or control subjects in studies.

We have examined the mortality risk using various analytical approaches which all yield similar conclusions, i.e., greater mortality risk in the ferric carboxymaltose group with point estimates of OR > 1 and RD > 0.

Stratified analysis allows for variations in the event rates at the study-level, thus accounting for the expected between-study heterogeneity from different patient populations. Demographics, baseline characteristics, and follow-up mechanisms were comparable between treatment groups within controlled trials. By limiting the analysis to the pooled controlled studies using stratified analysis, the problems of pooled analysis - "significantly greater numbers of subjects treated with ferric carboxymaltose, significantly longer follow-up for subjects treated with ferric carboxymaltose and significantly greater baseline risk of death in the ferric carboxymaltose group" as suggested by the sponsor should be largely controlled.

Several limitations in the clinical database cannot be handled by the statistical analysis. The number of studies and study subjects were limited for each indication, so that we were not able to assess the mortality risk by indication. The study drug exposure between treatment groups within trials cannot be compared directly due to the different routes of administration, i.e., injection versus oral intake. The 95% confidence intervals were very wide due to the small sample sizes in the studies. If there was one additional or one fewer death in either group, the conclusions may change dramatically. For instance, if FER-CARS-01 study were not included in the analysis, the point estimate of OR (95% CI) using Peto's method would be 6.17 (1.21, 31.46) showing a significant difference in mortality risk. Additional safety data from further studies are needed in order to better quantify the mortality risk and to fully investigate the safety signal arisen from the current clinical database.

6. References

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7. Appendix I

The list of the 13 completed and ongoing clinical studies included for the safety evaluation by the medical reviewer

		Treatment group	
Study population	Study design	Ferinject # of deaths/# of subjects (%)	Control(oral iron/Venofer/placebo) # of deaths/# of subjects(%)
Completed studies			
Post-partum anemia			
1VIT03001	Open-label,multicenter, R, multiple-dose, AC	1/174(0.57%)	0/178
VIT-IV-CL-009		0/227	0/117
1VIT06011		0/142	0/147
Heavy uterine bleeding			
1VIT04002/04003	Open-label,multicenter, R, multiple-dose, AC	0/230	0/226
Inflammatory bowl dz			
VIT-IV-CL-008	Open-label,multicenter, R, multiple-dose, AC	1/137(0.73%)	0/63
VIT-IV-CL-003	Open-label,multicenter, multiple-dose, uncontrolled	0/46	
Hemodialysis			
VIT-IV-CL-015	Open-label, multicenter, R, multiple-dose, AC	1/119(0.84%)	0/118
VIT-53214	Open-label,multicenter, multiple-dose, uncontrolled	2/162(1.23%)	
Iron deficiency anemia			
1VIT05006	Single-dose, cross-over	1/584(0.17%)	0/569
VIT-IV-CL-02	Single-dose, PK, safety	0/24	0/8
VIT-IV-CL-001	Single-dose, PK, safety	0/6	
Ongoing studies			
Non-HD CKD			
1VIT04004	Open-label,multicenter, R AC	2/147(1.36%)	0/101
1VIT05005	Long-term extension of 1VIT04004	2/127(1.57%)	
Restless leg syndrome			
1VIT05009	blinded, multicenter, R, placebo-controlled		