Complete Supporting Documentation From the Clinical Development Program on the Efficacy and Safety of Ferric Carboxymaltose Injection (FCM)

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PREFACE FOR THE REVIEWER

This document consists of two parts. The Advisory Committee Overview parallels as closely as possible the presentation Luitpold will deliver to the committee. It is designed to cover the key claims for FCM as well as the key issues raised by the FDA in its review. The Supporting Information document that follows is a summary of the data and interpretations upon which the submission of Ferric Carboxymaltose (FCM) is based.

The primary focus of the questions raised by the FDA review is mortality. Accordingly a large section of both the Overview and the Supporting Information presents the data on and discussion of mortality. In the Overview and in the Luitpold presentation, this discussion comes toward the end in order to first present the context of the patient population and the study results. In order to present as comprehensive a view of mortality as possible, a supplemental analysis and discussion of mortality can be found in Appendix B in the Supporting Information section.

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1.0 Ferric Carboxymaltose Advisory Committee Overview

This document consists of two parts. This Overview parallels as closely as possible the presentation the sponsor will give to the committee. It's designed to cover the key claims made by the sponsor as well as the key issues raised by the FDA in its review.

The reference numbers in this section in parentheses refer to sections in the Supporting Information, which begins with Section 2.0. These sections provide a summary of the data and interpretations upon which the submission of Ferric Carboxymaltose (FCM) is based.

There is an appendix (Appendix B) devoted to a detailed overview and discussion of mortality.

Medical Need

Iron deficiency with or without anemia has many adverse effects on the nervous system, physical activity, and immune response. Iron Deficiency Anemia is found throughout the reproductive age span, but the disease burden that is present in postpartum women and women with Heavy Uterine Bleeding (HUB) has important clinical consequences. Depending on the severity of blood loss, anemic postpartum patients may present with increased clinical morbidity, including cardiovascular symptoms, dizziness, fatigue, infections, lactation problems and a need for a prolonged hospitalization. Anemia due to heavy or otherwise abnormal uterine bleeding can cause fatigue, mood disorder, significant discomfort, and loss of work time. Clinical consequences of HUB and anemia include increased emergency department visits, gynecology referrals, RBC transfusions, surgeries (myomectomies and hysterectomies), and delayed definitive operative treatments because of suboptimal hemoglobin (Hb) levels.

Ferric Carboxymaltose

FCM, a stable Type I polynuclear iron (III)-hydroxide carbohydrate complex, was chosen for development as iron replacement therapy for the treatment of iron deficiency anemia (IDA) because it offers important clinical advantages compared to other currently available iron therapies. FCM has been recently approved in 19 countries outside the US for the treatment of IDA when oral iron preparations are ineffective or cannot be used. FCM has recently been launched in Germany, but as of the date of this report, market launch has not occurred in any other country.

The aim of FCM treatment is to return both hemoglobin and iron stores (serum ferritin) to normal levels. Although oral iron therapy is usually the first choice for iron repletion, intravenous iron supplementation is indicated in some clinical situations. Current iron therapies are generally effective for the treatment of IDA although they have some clinical characteristics that limit their use.

Limitations of Current Therapy (2.2.2)

Oral iron, which is the primary treatment for IDA, is limited by its tolerability due to GI side effects and resulting problems with compliance or adherence. In addition, it is not easily absorbed and variations in bioavailability are common between available agents. In certain patients iron loss and iron utilization exceed the rate of iron store replacement possible with oral iron.

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First generation intravenous irons, like iron dextran that carries a Black Box Warning, provide a potentially dangerous clinical alternative to oral iron. Iron Dextran carries the risk of severe immunological responses, sometimes resulting in fatal anaphylaxis, and delayed hypersensitivity-like reactions (arthalgia, myalgia, fever) at the doses that are necessary to provide the desired clinical benefit. Intravenous iron dextran continues, however, to be used in the treatment of IDA of multiple etiologies even though hospitalization and death due to anaphylaxis are still reported and despite the FDA's recommendation that resuscitative medication and personnel trained in anaphylaxis resuscitation be available at the time of treatment.

Second generation, non-dextran intravenous irons like iron sucrose and ferric gluconate do not contain the dextran moiety, but they have significant dosage and administration rate limitations. They can be characterized by a significant risk of bioactive reactions at higher doses and, importantly, by dose limits that require multiple infusions. Bioactive iron reactions are characterized by hypotension that may be clinically significant but without allergic signs and pain in chest, abdomen or flank, and nausea, vomiting and diarrhea. All 3 current i.v. iron treatments are limited by dosing regimens that render the effectiveness of treatment problematic for many of those suffering from certain kinds of IDA.

Benefits of FCM (2.2)

Because FCM is an intravenous iron with a simple dosing regimen, there is no issue, as there is with oral iron, with patient follow up or with patients not following prescribing information due to adverse events. In contrast to first generation intravenous irons, FCM does not contain dextran or modified dextrans nor does it react with dextran antibodies; therefore, the risk of anaphylaxis/hypersensitivity reactions is low compared to iron dextran and its derivatives. Due to its structure, FCM is more stable than the second generations irons, ferric gluconate and iron sucrose, making it possible to administer much higher single doses safely over shorter periods of time, a clinical requirement for an effective intravenous iron treatment in non-dialysis populations.

The larger FCM doses result in less frequent administration of intravenous iron that would benefit, in particular, severely iron deficient and anemic populations such as those who are postpartum or have heavy uterine bleeding (HUB). To be treated with currently available intravenous iron agents, the average postpartum and HUB patient would require an initial test dose, followed by 10-20 doses of iron dextran as labeled, each accompanied by personnel equipped and trained for resuscitation of anaphylaxis; 8-16 doses of ferric gluconate; or 3-5 doses of iron sucrose by prolonged (2.5 hours) intravenous infusion. Ferric gluconate and iron sucrose are not approved for the treatment of IDA in the postpartum and HUB populations. In contrast, approximately 92% of the FCM-treated patients required 1 (5%) to 2 (87%) doses administered over 15 minutes.

FCM Trial Program (2.3)

The aim of the overall development program was to demonstrate the safety and effectiveness of intravenous FCM in the treatment of IDA. Because IDA affects many different patient populations, Luitpold conducted twelve multicenter trials in a variety of patient populations. After reviewing the entire program, the company decided to take a controlled, stepwise approach to the development of FCM. Accordingly this submission has been limited to the postpartum and

HUB patient populations, the populations in which Luitpold conducted the most rigorous and comprehensive trials.

A total of 2050 subjects received at least 1 dose of FCM across the 12 multicenter trials. An additional 30 subjects received at least 1 dose of FCM in 2 single-center pharmacokinetic studies. The studies conducted in the FCM program are outlined below.

Women's Health (1052 patients)

- Postpartum (700) and heavy uterine bleeding (HUB) (352)

Other Iron Deficiency Anemias (1028 patients)

- Hemodialysis, gastrointestinal disorders including inflammatory bowel disease (IBD), non-dialysis dependent chronic kidney disease (CKD), heart failure, and various underlying conditions

FCM Study Outcomes: Efficacy (2.5) and Safety (2.6)

The postpartum and HUB studies demonstrated the superiority of FCM to oral iron in the treatment of iron deficiency anemia:

- The proportion of subjects who achieved a hemoglobin >12.0 g/dL anytime during the study was statistically significantly greater in the FCM group compared with the oral iron group in postpartum Studies VIT-11 and VIT-01 and HUB Study VIT-02/VIT-03

- The proportion of subjects who achieved an increase in hemoglobin ≥3.0 g/dL anytime during the study was statistically significantly greater in the FCM group compared with the oral iron group in postpartum Studies VIT-11 and VIT-01 and HUB Study VIT-02/VIT-03

- The proportion of subjects who achieved an increase in hemoglobin ≥2.0 g/dL anytime during the study was statistically significantly greater in the FCM group compared with the oral iron group in HUB Study VIT-02/VIT-03

- The proportion of subjects who achieved the primary endpoint in each study was first demonstrated statistically at Day 7 (VIT-01 and VIT-02) or Day 14 (VIT-11) suggesting that FCM may be especially useful in patients who require rapid correction of Hemoglobin (e.g., pre-surgical patients).

- The clinical benefit of FCM was observed across demographic and baseline characteristics

Key safety findings from the women's health studies were:

- The incidence of gastrointestinal disorders was higher in the oral iron group (29.9%) compared to the FCM group (11.9%), while the incidence of adverse events associated with skin and subcutaneous tissue disorders was higher in the FCM group (6.6%) compared to the oral iron group (2.5%).

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- The overall incidence of adverse events resulting in premature discontinuation of study drug was 1.7% in the FCM group and 1.9% in the oral iron group.

- The overall incidence of serious adverse events was 1.7% in the FCM group and 1.6% in the oral iron group. None of the serious adverse events experienced in the postpartum/HUB studies was considered related to study drug administration.

- Decreases in serum phosphate were observed following FCM and, to a lesser extent, oral iron treatment. Phosphate experts who have reviewed all the phosphate data from the development program consider the decrease in phosphate to be interesting but clinically not important in the target populations and recommend that patients with a likelihood of baseline hypophosphatemia (malnutrition, etc) have serum phosphate measured on the day of FCM infusion and take appropriate dietary supplements if low. These decreases:

    - are transient, resolving over an average of 18 days
    - have slow onset with maximum declines at 14 days
    - occur commonly, with a high incidence in the HUB population
    - are asymptomatic with no adverse effect of lower post-treatment values on the adverse event or serious event rate and
    - are not associated with other electrolyte changes

Safety findings from combined parallel-group, oral iron controlled studies were similar to that for the women's health studies. In the parallel-group, iron sucrose controlled studies, there were no clinically important safety differences between FCM and iron sucrose.

Review of Mortality (Appendix B)

Eleven deaths were reported in the FCM development program. All eleven deaths were judged by Investigators to be unrelated to study drug treatment.

In the postpartum and HUB controlled trials there was 1 death attributed to peripartum cardiomyopathy in the VIT-01 postpartum trial. In the FCM-controlled trials enrolling across multiple indications, there were 5 deaths reported in the FCM arm including the 1 mentioned above. Three of the 4 non-women's health deaths were in CKD patients, and 1 was in an IBD patient. These 4 deaths included 1 acute myocardial infarction (hemodialysis) and 1 cardiac arrest. There was 1 congestive heart failure death reported in the control arm.

In the uncontrolled trials there were 5 deaths reported, 4 in the CKD populations and 1 in IDA. The etiology of these deaths was variable and without indication of any pattern.

Luitpold convened an external group of experts to review the deaths to assess possible causality of FCM treatment. The panel considered the possible relationship of dose, time between dose and event, phosphate levels, and reported cause of death. In addition separate experts reviewed the deaths for possible bias. These reviews led to a consensus conclusion that there is no apparent causal relationship between FCM treatment and mortality.

Treatment group comparisons for deaths accounted for treatment group differences in numbers of subjects and length of observation, as well as treatment group differences in the baseline (intrinsic) mortality risk. There were over twice as many subjects exposed to FCM as control

groups and the length of observation for FCM was over twice that of oral iron. Patient demographics, as well as the intrinsic risk of death varied substantially across the patient populations included in the development program. Treatment group comparisons were thus made in combinations of randomized controlled studies with populations of similar intrinsic mortality risk. Key findings were:

- Observed treatment group differences in mortality were small and within statistical expectation.
    - The mortality rates in women's health studies were similar for FCM (0.13% incidence or 0.87 deaths per 100 patient years) and oral iron (0 incidence).
    - The mortality rates in other parallel-group, controlled studies were similar for FCM (0.88% incidence or 5.28 deaths per 100 patient years) and control (0.3% incidence or 1.96 deaths per 100 patient years). These studies included higher risk subjects with CKD and heart failure.
    - The mortality rate was related primarily to the baseline mortality risk of the clinical trial populations (e.g., mortality rates were greater in CKD than in women's health).
- Anaphylaxis, bioactive iron reactions, rate of hemoglobin rise, hemoglobin >13 g/dL, hypophosphatemia, and FCM dose were not associated with the incidence of death.
- There was no unifying pattern of mortality, mechanism of action, or dose response.

The heterogeneity of intrinsic mortality risk across populations and the low observed incidence rates of death within populations minimize the value of statistical comparisons and indicate the need for a thorough clinical review of each death to assess potential causality. The multiple external, independent experts drew the following conclusions about the individual deaths:

- No death was consistent with any known adverse effect of FCM or any intravenous iron agent at any dose or any rate of administration
- No death was consistent with any known pharmacokinetic and pharmacodynamic characteristics of FCM or any class of iron agent
- No deaths shared significant features with other deaths except for the frequent finding of a high comorbid disease burden that is characteristic of the study population
- No death lacked explanation

Basis for Submission

Luitpold's request for approval of FCM is based on the following conclusions:

FCM provided superior and earlier correction of anemia to oral iron in the HUB and postpartum populations with fewer infusions than would be required for other intravenous iron products. The safety and tolerability profile for FCM was similar to that of oral iron and iron sucrose with no serious hypersensitivity, no symptomatic hypotension, and no bioactive iron reactions.

Furthermore, it is safer at higher doses over shorter periods of time than possible with other intravenous iron agents therefore allowing more practical dosing. FCM provides substantial benefits over current iron treatments without their dosing and safety risks and limitations.

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Overview Table

Product	"FCM" (ferric carboxymaltose injection), Injectafer®
Proposed Indication	FCM is a hematinic agent indicated for the treatment of iron deficiency anemia (IDA) in **Postpartum** and **Heavy Uterine Bleeding** patients.
Proposed Target Populations	Patients with IDA secondary to Postpartum or Heavy Uterine Bleeding who: • Need a more rapid and predictable recovery of hemoglobin than can be provided by oral iron, • Have ongoing blood loss greater than the rate of repletion reasonably achievable with oral iron treatment; • Require relief of anemia-related symptoms or dysfunction more rapidly than could be achieved by oral iron treatment or in patients intolerant or non-adherent with oral treatment regimens.
Proposed Dosing Schedule	• FCM is administered intravenously either by IV push injection or by IV infusion over 15 minutes • The dose is determined by calculating the total iron requirement and dividing this total amount into one or more single dose(s). • Maximum single dose must not exceed 15 mg/kg per dose or 1,000 mg, whichever is lower. • Administer the single doses every 7 days until the total iron requirement or a maximum of 2,500 mg is reached.
Efficacy Response	Met all pre-defined primary endpoints in all randomized controlled studies. Clinically and statistically significant increases in Hb in all randomized controlled studies.
Safety	**Postpartum / HUB studies:** Adverse Events: FCM 47.5% oral iron 53.1% Serious Adverse Events: FCM 1.7% oral iron 1.6% No Serious Adverse Event was judged related to FCM **Postpartum/HUB Mortality:** 1 unrelated death out of 1052 FCM exposed subjects **All Controlled Studies** 5 unrelated deaths out of 1230 FCM exposed subjects 1 unrelated death out of 1002 control subjects **All Uncontrolled Studies** 5 unrelated deaths • No death was consistent with adverse effects of FCM or any intravenous iron agent at any dose or any rate of administration • No death was consistent with any known pharmacokinetic and pharmacodynamic characteristics of FCM or any class of iron agent • No deaths shared significant features with other deaths except for the frequent finding of a high comorbid disease burden that is characteristic of the study population • No death lacked explanation

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2.0 Supporting Information

2.1 Introduction to Ferric Carboxymaltose Injection (FCM)

Luitpold Pharmaceuticals has been a leader in the development of IV iron products since the development and introduction of Dexferrum® (iron dextran injection) in 1996 indicated for the treatment of iron deficiency anemia in all patient populations. Its 2nd generation product, Venofer® (iron sucrose injection) is marketed solely for the treatment of iron deficiency anemia in non-dialysis and dialysis dependent chronic kidney disease patients.

FCM is the first 3rd generation intravenous iron. It is a stable Type I polynuclear iron (III)-hydroxide carbohydrate complex developed as an intravenous iron replacement therapy for the treatment of iron deficiency anemia (IDA). After intravenous administration, FCM is mainly found in the liver (in the reticuloendothelial system [RES]), spleen, and bone marrow. The iron slowly dissociates from the complex and can be efficiently used in the bone marrow for hemoglobin synthesis. The carbohydrate moiety of FCM is metabolized by the glycolytic pathway. FCM has been very recently approved in 19 countries outside the US for the treatment of IDA when oral iron preparations are ineffective or cannot be used (**Table 1**). As of the date of this report, FCM has only been launched in Germany.

Table 1. Countries Where FCM Has Regulatory Approval

Austria	Ireland	Slovak Republic
Czech Republic	Latvia	Spain
Denmark	Lithuania	Sweden
Estonia	Luxembourg	Switzerland
Finland	The Netherlands	United Kingdom
Germany	Poland	
Greece	Portugal	

Ferric carboxymaltose offers significant advantages compared to other available intravenous iron preparations. It does not contain dextran or modified dextrans nor does it react with dextran antibodies; therefore, the risk of anaphylactoid/hypersensitivity reactions is very low compared to iron dextran and its derivatives. Unlike iron sucrose, FCM has a nearly neutral pH (5.0 to 7.0) and physiological osmolarity. It is more stable than ferric gluconate and iron sucrose, producing a slow delivery of the complexed iron to endogenous iron binding sites and has an acute toxicity in animals 1/5 that of iron sucrose. These characteristics of FCM make it possible to administer much higher single doses over shorter periods of time than ferric gluconate or iron sucrose, resulting in the need for fewer administrations to correct anemia and replete iron stores. Consequently, FCM is much better suited for outpatient use (**Table 2**).

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Table 2. Administration of 1600 mg of Intravenous Iron for Currently Available Iron Preparations and FCM

Iron Preparation	Test Dose Required	Maximum Approved Infusion Dose	Infusion Time	Number of Infusions
Iron dextran	Yes	100 mg	2 minutes	16 + test dose
Ferric gluconate	No	125 mg	10 minutes	13
Iron sucrose	No	200 mg	5 minutes	8
Iron sucrose	No	400 mg	2.5 hours	4
FCM	No	1000 mg	15 minutes	2

Intravenous iron is not like erythropoiesis stimulating agents (ESA), where higher ESA doses result in higher hemoglobins. Administration of iron does not stimulate erythropoeiesis, but rather enables erythropoiesis to achieve normal hemoglobin levels. Thus, iron therapy in any form cannot generate hemoglobin levels above what is physiologically normal for the patient, and therefore cannot generate "excessive" hemoglobin levels. With intravenous iron, excess iron not needed to achieve a hemoglobin normal for that individual is stored and released slowly as needed for erythropoiesis.

All intravenous iron agents are colloids with spheroid particles consisting of carbohydrate shells with ferric oxyhydroxide cores. Therapeutic efficacy of intravenous iron agents depends on uptake of the circulating agent by macrophages of the RES, principally in the liver. Iron is then mobilized slowly from the engulfed particles and released over days, weeks, and months from the macrophage to bind to circulating transferrin. Utilization of the iron dose is most rapid and complete in patients with severe iron deficiency. Since all intravenous iron agents share the same fundamental chemistry, and all depend on RES uptake of iron agent prior to delivery of iron to erythroid marrow, they are distinguished in clinical practice by the rate that a maximum single dose can be safely administered and the adverse events and serious adverse events associated with their administration.

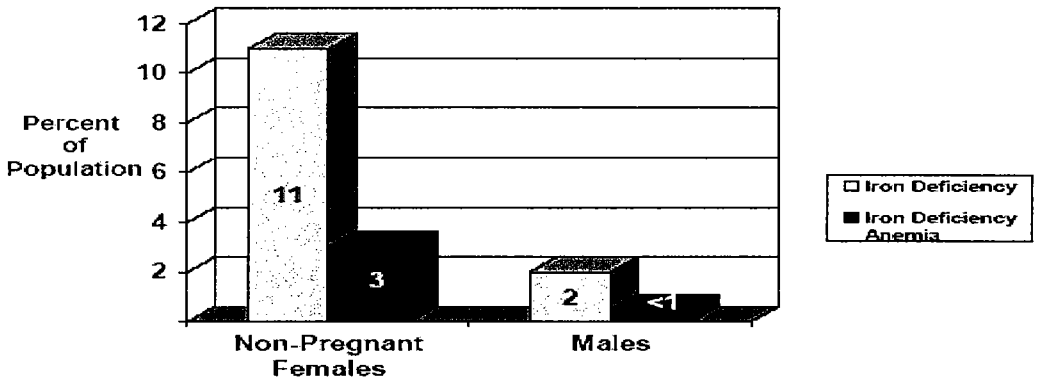
2.2 Medical Need in Postpartum and Heavy Uterine Bleeding (HUB) Patients

2.2.1 Overview & Epidemiology

Anemia is more prevalent in reproductive age women who generally have smaller baseline iron stores than men (**Figure 1** and **Figure 2**). These women are at risk for developing iron deficiency anemia (IDA) because of inadequate dietary intake of iron, increased loss/need of iron, and failure of oral iron therapy. Only 1 in 4 women get the US RDA of 18mg iron per day. Healthy People 2010, an initiative from the US Health and Human Services Secretary and the US Surgeon General, identified IDA in females of reproductive age and in pregnant women as public health issues where prevention and treatment interventions are much needed. IDA afflicts 3-6% of the 60 million women of reproductive age in the United States.[1,2,3,4] The magnitude of the quality of

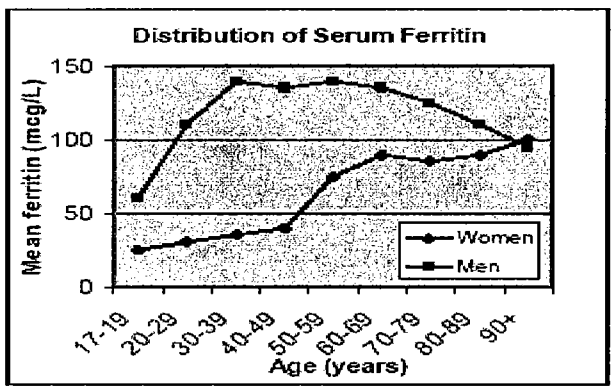
life deficits suffered by women with IDA is frequently underestimated as anemic women are unlikely to spontaneously report anemia-related symptoms.[6]

Figure 1. Prevalence of IDA by Gender



Iron Deficiency Anemia - United States, 1999-2000, MMWR October 11, 2002/51(40):897-899

Figure 2. Distribution of Serum Ferritin by Gender



Adapted from Zacharski Am Heart J 2000;140:98-104

Although IDA is found throughout the reproductive age span, the disease burden that is present in postpartum women and women with HUB has important clinical consequences. Data from the National Health and Nutrition Examination Survey (NHANES, 1988-1994) indicated that IDA was prevalent in 4.2% of postpartum women in the U.S. Depending on the severity of blood loss, anemic postpartum patients may present with increased clinical morbidity, including cardiovascular symptoms, dizziness, fatigue, infections, lactation problems and a need for a prolonged hospitalization.[7]

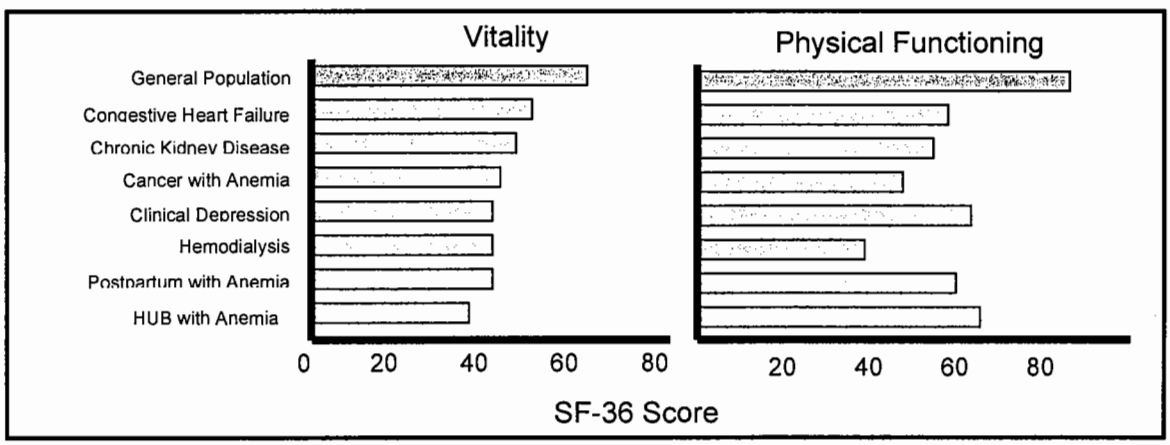
Anemia due to HUB can cause fatigue, mood disorder, significant discomfort, and loss of work time. Approximately 10-15% (6.6-10.3 million) of women experience HUB during their lifetime. Women with HUB are vulnerable to chronic anemia from iron deficiency and about 20% (1.3-2.1 million) will develop some level of anemia. Clinical consequences of HUB and anemia are increased emergency department visits, gynecology referrals, RBC transfusions, surgeries

(myomectomies and hysterectomies), and delayed definitive operative treatments because of suboptimal Hb levels. In reported studies of objective measurements of blood loss in HUB, as high as 83% of women suffering from HUB due to uterine fibroids had >80 ml (normal menstrual blood loss is <40 ml) of menstrual blood loss[8].

It is unknown what percentage of women with HUB experience anemia that cannot be sufficiently regulated by oral iron and that leads to these significant consequences. Current approximations are calculated by conservatively estimating that 40% of these women fail oral iron therapy. This means 520,000 to 840,000 women with anemia due to HUB may require treatment options other than oral iron therapy.

The extent of the clinical implications associated with anemia in these populations can be seen in the results of an assessment of health-related quality of life using a standardized tool. This assessment reveals that women with postpartum or HUB iron deficiency anemia (detected at baseline in postpartum study 1VIT3001 or HUB study 1VIT4002-03) report Physical Functioning and Vitality scores that are comparable to those seen in patients with other serious chronic diseases such as CHF and chronic kidney disease patients (**Figure 3**)[9,10,11].

Figure-3. SF-36 Vitality and Physical Functioning scores in women with postpartum anemia or anemia associated with heavy uterine bleeding (HUB) compared to scores seen in patients with other chronic illnesses.



2.2.2 Limitations of Current Iron Therapies & Need for New Options

Therapy for IDA in postpartum and HUB patients consists of the repletion of the iron deficits through the oral or parenteral route and treatment of the underlying disease.[7,12] The aim of treatment is to return both Hb and iron stores (serum ferritin) to normal levels.

Oral iron therapy is not effective in all patients. Causes of oral iron failure include:

- poor oral bioavailability;
- intolerance to long-term oral iron regimen due to GI side effects (nausea, constipation, and abdominal discomfort) – of particular concern to postpartum women;

- clinical conditions associated with iron malabsorbtion (e.g., inflammatory states with increase hepcidin, GI tract surgery/diseases);
- chronic iron loss and/or utilization exceeding the rate of replacement of iron stores possible with oral treatment (e.g., HUB and pregnancy/delivery).

High rates of non-adherence to oral iron regimen have been reported even in highly motivated pregnant patients- 10% after 2 weeks, 25% after 1 month, and up to 32% after 2 months of therapy.[13,14]

A successful intravenous iron preparation needs to be able to effectively deliver iron to the iron transport and storage proteins (transferrin and ferritin) without a significant risk of toxic, free radical species being formed. To achieve this, intravenous iron products contain iron in a stable ferric state (often as iron (III)-hydroxide) as complexes within a carbohydrate polymer. Pharmacologic properties of the complexes vary because of the differences in the chemical interaction between the iron core and outer carbohydrate polymer. This chemical interaction controls the rate of release of the 'bioactive' form of iron for transfer to transferrin and/or iron storage compartments. Intravenous iron agents share similar core iron chemistry but differ by core size, carbohydrate composition and strength of the carbohydrate-core iron bond. The risk of a bioactive iron reaction is related to particle chemistry, particle size, and the dose and rate of intravenous iron infusion. Bioactive iron reactions are characterized by hypotension, pain in the flank, abdomen or chest, and nausea, vomiting or diarrhea. The optimal release rate should be slow enough to avoid 'bioactive' iron transfer into the intra- and extracellular spaces, which can precipitate bioactive iron reactions.

There is a considerable body of efficacy and safety experience available for marketed intravenous iron preparations. Currently in the US, the only IV iron indicated and labeled for the treatment of IDA is iron dextran (InFed®, Dexferrum®). Its well-known association with fatal, severe life-threatening anaphylactic reactions prompted the FDA to require a Black Box Warning (**Figure 4**) for these products, cautioning medical practioners of these reactions and requiring availability of resuscitative medications and personnel trained in resuscitation techniques. Because of the risk of this severe reaction it has been limited to second line therapy and practioners have largely limited its use to hospitalized patients. The use of iron dextran in other patient populations such as those with IDA associated with the postpartum state or HUB appears to be virtually non-existent despite a compelling medical need for rapid and safe replenishment of body iron. Additionally, FDA approved labeling for these products also include requirements for the administration of a test dose prior to infusion.

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Figure 4. Iron Dextran Black Box Warning.

WARNING

THE PARENTERAL USE OF COMPLEXES OF IRON AND CARBOHYDRATES HAS RESULTED IN ANAPHYLACTIC-TYPE REACTIONS. DEATHS ASSOCIATED WITH SUCH ADMINISTRATION HAVE BEEN REPORTED. THEREFORE, DEXFERRUM SHOULD BE USED IN ONLY THOSE PATIENTS IN WHOM THE INDICATIONS HAVE BEEN CLEARLY ESTABLISHED AND LABORATORY INVESTIGATIONS CONFIRM AN IRON DEFICIENT STATE NOT AMENABLE TO ORAL IRON THERAPY. BECAUSE FATAL ANAPHYLACTIC REACTIONS HAVE BEEN REPORTED AFTER ADMINSTRATION OF IRON DEXTRAN INJECTION, THE DRUG SHOULD BE GIVEN ONLY WHEN RESUSCITATION TECHNIQUES AND TREATMENT OF ANAPHYLACTIC AND ANAPHYLACTOID SHOCK ARE READILY AVAILABLE.

Despite these FDA warnings and test dose requirements, hospitalizations and deaths after iron dextran have been reported [16,17,67,68] severely limiting its use as a therapeutic option to oral iron failure.

The 2nd generation intravenous iron products (iron sucrose and ferric gluconate) do not contain the dextran moiety, and the incidence of anaphylaxis and anaphylactoid reactions with these products is markedly lower.[15,16] However, because of the smaller size of the iron core and the weaker bonding between the core and the carbohydrate shell, ferric gluconate and iron sucrose have significant dosage and administration rate limitations in order to avoid the adverse symptoms of bioactive iron reactions.

While hemodialysis (HD) patients require chronic iron therapy, their routine venous access for HD allows frequent administration of low doses of intravenous iron products. However, larger doses resulting in less frequent administration of intravenous iron would benefit other populations with marked iron deficiency such as those who are postpartum or have HUB. To be treated with the only approved intravenous iron agents for IDA, the average postpartum and HUB patient with an iron repletion requirement of 1600 mg [20] would require an initial test dose, followed by >16 doses of iron dextran as labeled (**Table 3**), each accompanied by personnel equipped and trained for resuscitation of anaphylaxis per FDA Black Box Warning.

Table 3. Administration of 1600 mg of Intravenous Iron for Currently Available Iron Preparations

Iron Preparation	Test Dose Required	Maximum Approved Infusion Dose	Infusion Time	Number of Infusions
Iron dextran	Yes	100 mg	2 minutes	16 + test dose
Ferric gluconate	No	125 mg	10 minutes	13
Iron sucrose	No	200 mg	5 minutes	8
Iron sucrose	No	400 mg	2.5 hours	4

Administration of currently available 2nd generation IV iron agents in this population would be outside the current labeled indications, and would require 13 doses of ferric gluconate or 4 doses of iron sucrose by prolonged (2.5 hours) intravenous infusion.

Although oral iron therapy is usually the first choice for iron repletion, a safer more convenient and effective intravenous iron supplementation is needed in patients with IDA secondary to postpartum or HUB who:

- Need a more rapid and predictable recovery of hemoglobin than can be provided by oral iron;
- Have ongoing blood loss greater than the rate of repletion reasonably achievable with oral iron treatment;
- Require relief of anemia-related symptoms or dysfunction more rapidly than could be achieved by oral iron treatment or in patients intolerant or non-adherent with oral treatment regimens.

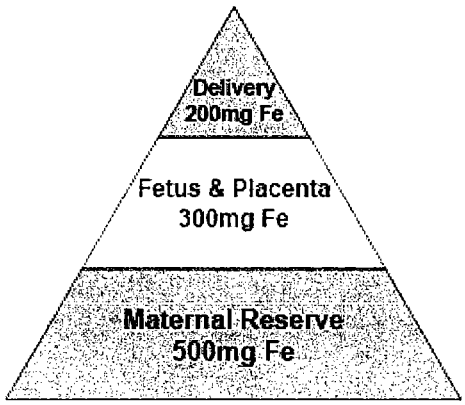
The medical need in treating postpartum IDA and IDA due to HUB could be met by a 3rd generation intravenous iron with shorter infusion time and fewer infusions. Fewer injections may reduce side effects such as sclerosing, infection, and extravasation associated with repeated venous administration. These attributes would lower barriers to IDA treatment in this population by reducing office visits; and providing higher adherence and more timely correction of anemia when compared to long a term oral iron regimen.

2.2.3 Clinical Significance of Postpartum Iron Deficiency Anemia (IDA)

Iron deficiency is precipitated during pregnancy because of the expansion of the red cell mass during the second trimester. Iron deficiency during pregnancy is compounded by preferential fetal utilization of iron from maternal iron stores. Blood loss during and after delivery, often while many women are taking prenatal vitamins containing iron, further contributes to postpartum anemia and iron deficiency.

Of the approximate 1 gram of elemental iron needed during pregnancy **(Figure 5)**, 300 mg is used for the fetus and placenta and 700 mg is added to the maternal Hb.[21]

Figure 5. Total Iron Requirements During Pregnancy is 1 gm (405 mg/dL) Fe



Approximately 200 mg is lost in bleeding during and after delivery. Therefore, the mother loses about 500 mg of iron with each viable pregnancy. Thus, an iron reserve of >500 mg is considered the minimum for pregnant women. A recent report indicates that only 20% of women of reproductive age have such an iron reserve, 40% have iron stores of 100-500 mg, and 40% have virtually no iron stores.[22] Although iron absorption increases with pregnancy, it is insufficient to prevent iron deficiency in at least 20% of women taking iron supplements.

Postpartum anemia is generally defined by a Hb <10 g/dL. Hemoglobin as low as <7 g/dL is a complication in 5% of births. Data from the National Health and Nutrition Examination Survey (NHANES 1988-1994) indicate that IDA was prevalent in 4.2% of all US women aged 20 to 40 who were 0 to 6 months postpartum.[23] It is estimated that 1 in 8 US women are iron deficient up to 12 months after delivery, and 1 in 12 women are iron deficient 13 to 24 months postpartum.[24]

In a retrospective cohort analysis of 59,428 participants in the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) in 12 US states, Bodnar et al. found that the prevalence of postpartum anemia was 27% among low income women regardless of racial and ethnic background. Anemia rates were much higher among Hispanic and black women, with a prevalence rate of approximately 1.5 and 2.3 times that of white women respectively[25].

Recent publications suggest a strong relationship between decreased iron status and depression, stress, and cognitive function. In a prospective, randomized, controlled, intervention trial conducted in mothers of full-term normal birth weight babies with postpartum follow-up at 10 weeks and at 9 months (n=81), treatment of IDA resulted in a 25% improvement ($p<0.05$) in depression and stress scales.[26] Other studies show that patients with postpartum anemia have more overall symptoms, more symptoms of "maternity blues" and a reduced sense of well being compared to non-anemic patients.[27,28] A longitudinal study of postpartum women showed that a low Hb level at 1 week postpartum was a significant risk factor for the development of postpartum depression.[29] Iron deficiency in the postpartum period may impair the ability to fully participate in childcare, household tasks and social activities. Iron deficiency may also diminish productivity in physical and intellectual work.[30] These issues potentially reduce the ability of the

woman to provide care for her newborn infant and retard her ability to resume her other usual activities. Therefore, treatment to restore normal Hb levels in a timely manner is important to these women, their families, and society as a whole.

The adverse effects of untreated IDA on maternal cognition, mood, and behavior in the postpartum period have shown to negatively impact maternal-infant interactions with lasting deleterious effects on early childhood development.[26] For example, mothers with IDA 10 weeks after parturition are less responsive to and more controlling of their infants than non-anemic mothers.[31] Infants of mothers with IDA are developmentally delayed at 10 weeks.[31] Importantly, developmental deficits in infants of iron deficient mothers may persist long after correction of maternal iron status.[31]

A recent analysis of the 2003 Healthcare Cost and Utilization Project Nationwide Inpatient Sample (HCUP-NIS) database, a nationally representative sample of all US women, demonstrated that among women giving birth, those with anemia in the setting of pregnancy and postpartum related bleeding were 9 times more likely to have received a blood transfusion (18% vs. 2%, P<0.0001), had 33% longer average length of hospital stay (4.1 days vs. 3.1 days, P<0.0001).[32]

Traditionally, the most common approach to the treatment of postpartum anemia has been oral iron supplementation and blood transfusions.[33,34] Oral iron supplementation is often effective and studies have shown benefits to the mother and her offspring who are treated for IDA during pregnancy and postpartum period. In some cases oral iron preparations, however, cannot be tolerated or are not sufficiently effective as noted above, and intravenous iron is a preferable choice.

Yet another alternative, blood transfusions, is a less safe choice because it carries serious safety concerns arising from the risk of either acute transfusion reactions or serious chronic viral infection. Blood transfusions in this patient population are uncommon, but not rare. Transfusions are administered in 0.3 to 1.7% of vaginal deliveries, between 0.7 and 6.8% of caesarean deliveries, and in as much as 8.6% of cases of ruptured ectopic pregnancies.[24] A gram increase in Hb requires approximately 1 unit of packed RBCs, an unsafe way of giving iron in a hemodynamically stable anemic patient. Blood transfusions carry the risk of febrile reactions, hemolytic reactions, anaphylaxis, graft vs. host disease, prolonged hospitalization as well as significant infectious risks. Clearly, avoidance of transfusions should be regarded a direct benefit to patients when assessing efficacy of iron therapy in postpartum anemia as well as the public health benefit of conserving blood supplies.

2.2.4 Clinical Significance of Heavy Uterine Bleeding (HUB) Iron Deficiency Anemia (IDA)

Premenopausal women with bleeding disorders represent an unmet medical problem.[35] Specifically, HUB (also known as excessive uterine bleeding, excessive menstral bleeding, dysfunctional uterine bleeding, or menorrhagia) is one of the most common and economically significant gynecologic complaints. HUB can result from organic causes such as systemic disease and reproductive tract abnormalities including uterine leiomyomata (fibroid), bleeding due to endocrine dysfunction, or less frequently, iatrogenic over anticoagulation. Untreated,

persistent HUB leads to negative iron balance, iron depletion, iron deficiency erythropoiesis and, eventually, IDA.

Population studies have shown that about 10% of women have HUB, which is menstrual blood loss of >80 mL per cycle (approximately 40 mL of menstrual blood is passed during the average period).[36] Women with HUB are at significant risk of developing IDA, and they often have a serum Hb level <12 g/dL. Up to two thirds of women with HUB have IDA or low serum ferritin level.[37] In another study of a cohort of women (N=115) with mean age of 35.4 years with a physician diagnosis of menorrhagia, forty-one percent were anemic at baseline (Hb < 12 g/dL).[38]

Uterine fibroids affect over 25% of reproductive aged women.[39] In a study by Menzies et al., about 20% of women with fibroids had hemoglobins <10.8 g/dL.[40] The relative risk of fibroids is two to threefold greater in black women than white women.[41] Fibroids are the most common indication for hysterectomy, accounting for 30% of hysterectomies in white women and over 50% of hysterectomies in black women.[42] Even when surgical interventions like myomectomy and hysterectomy are indicated for HUB secondary to uterine fibroids, delays or cancellations of interventions can occur if preoperative Hb is unacceptably low. Because HUB and symptomatic IDA are prominent symptoms prompting hysterectomy for fibroids, they are significant contributors to elevated hysterectomy rates in susceptible populations.

Women with anemia associated with HUB face substantial risk of blood transfusion. Analysis of the 2003 HCUP-NIS database demonstrated that among women hospitalized due to HUB, those with anemia were more likely to have received a blood transfusion (24% vs. 0.7%, P<0.0001). Twenty-seven percent of these women (vs. 3.2%, P<0.0001) with anemia due to HUB had emergency department admission.[43]

Several randomized double-blind, placebo-controlled trials in women of childbearing age have shown that iron deficiency with anemia impairs, and iron therapy improves, aerobic fitness, endurance capacity and fatigue.[44,45,46] Several trials and observational studies in these women show that iron deficiency negatively impacts cognition, and that iron supplementation had a positive effect on cognitive function.[47,48,49] Persistent IDA has an adverse social and economic impact on these women, their families, and their employers.[50]

Some of the women with anemia associated with HUB will benefit from oral iron supplementation. As with the postpartum population, oral iron supplementation or other IV iron formulations may not be appropriate due to adherence concerns or a need for a more rapid clinical response than is otherwise available. With approximately 74 million women aged 15-49 in the U.S. (U.S. Census 2006 Dataset), about 7 million women of reproductive age (or 10%) would have HUB.[51] About 3 million of this population of women with HUB would have anemia at baseline (based on estimates of 41%).

2.3 Trial Program

The aim of the development program was to demonstrate the safety and effectiveness of intravenous FCM in the treatment of IDA. Because IDA affects many different patient populations, Luitpold conducted twelve multicenter trials in a variety of patient populations. After reviewing the entire program, the company decided to take a controlled, stepwise approach to the development of FCM. Accordingly, this submission has been limited to the postpartum and HUB patient populations; therefore, the focus of this document will be on the studies

conducted in the postpartum and HUB populations with supplemental information presented from the other populations studied and continuing to be studied. The studies conducted in the FCM program are outlined below.

Iron Deficiency Anemia in Women's Health (Postpartum and Heavy Uterine Bleeding – 1052 patients)

- postpartum (Studies VIT-11 [1VIT06011], VIT-01 [1VIT03001], VIT-09 [VIT-IV-CL-009] and VIT-06 [1VIT05006]) – 700 patients
- heavy uterine bleeding (Study VIT-02/VIT-03 [1VIT04002/1VIT04003] and VIT-06 [1VIT05006]) – 352 patients

Iron Deficiency Anemias in other populations – 1028 patients:

- hemodialysis (Studies CL-15 [VIT-IV-CL-015] and VIT-53214 [VIT-53214])
- gastrointestinal disorders (Studies CL-03 [VIT-IV-CL-03] and CL-08 [inflammatory bowel disease; VIT-IV-CL-008])
- non-dialysis dependent CKD (Studies VIT-04 [1VIT04004] and VIT-05 [1VIT05005])
- heart failure (Study CARS [FER-CARS-01])
- various underlying conditions (Study VIT-06)
- Pharmacokinetic/Pharmacodynamic Studies:
    - subjects with mild IDA (Study CL-02 [VIT-IV-CL-02])
    - subjects with IDA or renal anemia (Study CL-01 [VIT-IV-CL-001])

Summaries of the number of subjects treated with FCM and comparators are presented for the women's health studies and all other IDA studies in **Figure 6** and **Figure 7**, respectively. Brief overviews of the multicenter studies are presented for the women's health studies and all other IDA studies in **Table 4** and **Table 5**, respectively. A total of 2050 subjects were exposed to FCM across the 12 multicenter trials. An additional 30 subjects were exposed to FCM in the 2 single-center pharmacokinetic studies. Of the 12 multicenter trials, 6 (Studies VIT-11, VIT-01, VIT-02/VIT-03, VIT-04, VIT-05, and VIT-06) were conducted by Luitpold in the US, Mexico, Canada, Hong Kong, Thailand, and Australia and 6 (Studies VIT-09, CL-15, VIT-53214, CL-03, CL-08, and CARS) were conducted by a European partner in Europe and Africa.

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Figure 6. Numbers of Subjects Treated With FCM or Oral Iron in Women's Health Studies

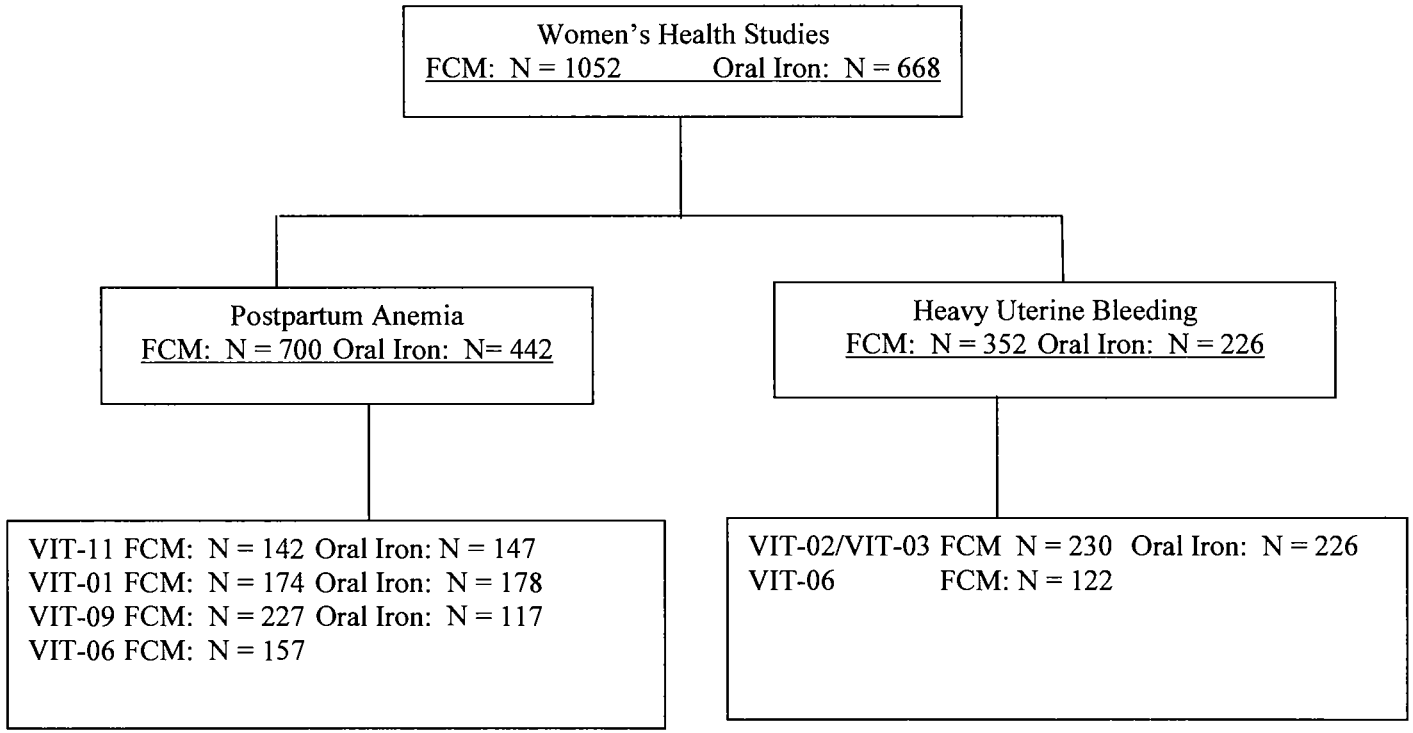

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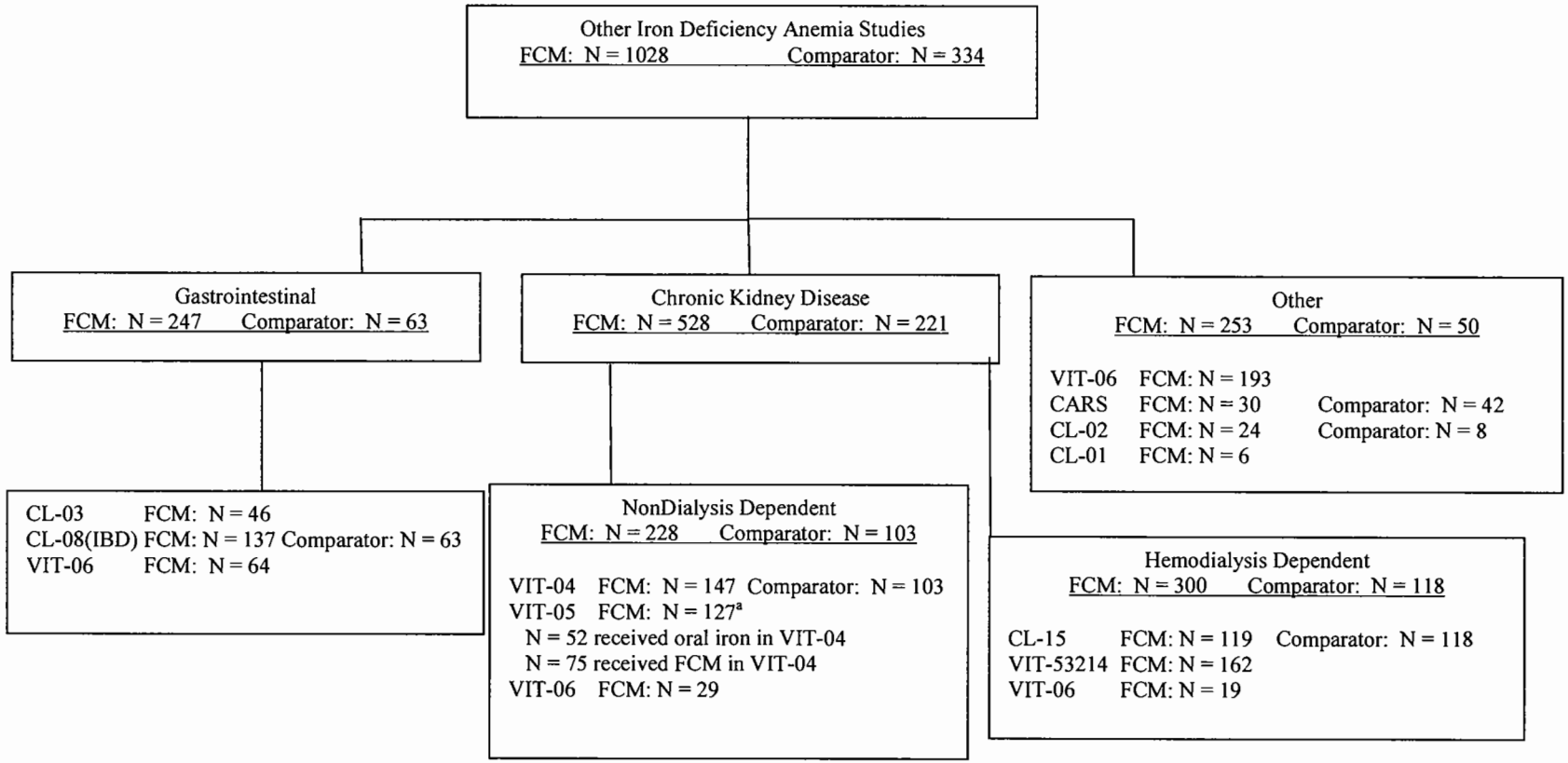
Figure 7. Numbers of Subjects Treated With FCM or Comparator in Other IDA Studies



a This was an extension study of VIT-04 in which 75 subjects were previously exposed and 52 subjects were new exposures.

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Four randomized controlled trials were conducted in women's health populations comparing FCM to oral iron. Three were studies of postpartum subjects and 1 was a study of HUB subjects, which was actually 2 separate studies that were combined for analysis. The study designs, numbers of subjects exposed, the study drug doses, and a brief presentation of the results are presented for each FCM study conducted in the women's health population in **Table 4**.

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Table 4. Summary of Clinical Studies of FCM in Women's Health Population

Study/ Center(s)/ # of Subjects	Design	Diagnosis and Criteria for Inclusion	Test Product Dosage Regimen Route of Administration and Duration of Treatment	Reference Therapy Route of Administration Duration of Treatment	Key Efficacy Results
Postpartum Anemia					
VIT-11 28 sites in the US Subjects: FCM: 142 Ferrous Sulfate:147 **For Details See 2.5.1 Pg 42**	Open-label, multicenter, randomized, multiple-dose, active-control study	Female subjects, postpartum within 10 days after delivery, with hemoglobin ≤10 g/dL at Baseline based on the average of 2 hemoglobin values drawn ≥18 hours postpartum.	A maximum of 1,000 mg (15 mg/kg) given at weekly intervals until the individual's calculated cumulative dose had been reached or a maximum of 2,500 mg had been administered.	Oral iron, 65 mg iron as ferrous sulfate TID for 6 weeks	**Primary:** **Hb >12 g/dL** FCM 91.4% Oral Iron 66.7% (p<0.0001) (95% CI: 15.20, 34.20) **Secondary:** **Hb increase ≥3 g/dL** FCM: 91.4% . Oral Iron:64.6% (p<0.0001) (95% CI: 17.08, 36.41)
VIT-01 43 sites in the US and Mexico Subjects FCM: 174 Ferrous Sulfate:178 **For Details See 2.5.2 Pg 49**	Open-label, multicenter, randomized, multiple-dose, active-control, study	Female subjects, postpartum within 10 days after delivery, with hemoglobin ≤10 g/dL at Baseline based on the average of 2 hemoglobin values drawn ≥18 hours postpartum.	FCM was dosed same as described for Study VIT-11	Oral iron, 65 mg iron as ferrous sulfate TID for 6 weeks	**Primary:** **Non inferiority** **Hb increase ≥2 g/dL** FCM:96.4% Oral Iron:94.1% (95% CI: -2.19, 6.88) **Secondary:** **Hb 12 g/dL** FCM 90.5% Oral Iron 68.6%(p<0.0001) (95% CI: 13.55, 30.12) **Hb increase ≥3 g/dL** FCM 86.3% Oral Iron 60.4%(p<0.0001) (95% CI: 16.93, 34.98)

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Table 4. Summary of Clinical Studies of FCM in Women's Health Population(continued)

Study/ Center(s)/ # of Subjects	Design	Diagnosis and Criteria for Inclusion	Test Product Dosage Regimen Route of Administration and Duration of Treatment	Reference Therapy Route of Administration Duration of Treatment	Key Efficacy Results
Postpartum Anemia					
VIT- 09 20 sites in Poland, Romania, and Russia Subjects FCM: 227 ferrous sulfate: 117 **For Details See 2.5.3 Pg 56**	Multicenter, open-label, randomized, active-controlled, multiple-dose study	Adult women ≥18 years old with postpartum anemia within 6 days after delivery.	A maximum of 1,000 mg iron (15mg/.kg) as IV FCM was given at weekly intervals up to 3 occasions until the calculated cumulative dose was reached.	Oral iron, 100 mg iron as ferrous sulfate BID for 12 weeks	**Primary non-inferiority Mean Change from baseline levels of Hemoglobin to Week 12** FCM: 3.4 g/dl Oral Iron:3.3 g/dl Lower bound of 95% CI was -0.07 g/dl with non-inferiority bound of –0.5 g/dl
Anemia of Heavy Uterine Bleeding					
VIT-02/VIT-03 84 sites in the US and Mexico FCM: 230 female subjects Oral Iron (ferrous sulfate): 226 female subjects **For Details See 2.5.4 Pg 58**	Open label, multiple-dose, multicenter, randomized, active-control study	Female subjects, ≥18 years of age with iron-deficiency anemia secondary to heavy uterine bleeding.	FCM was dosed same as described for Study VIT-11	Oral iron, 65 mg iron as ferrous sulfate TID for 6 weeks	**Primary:** **Hb increase ≥2 g/dL** FCM 82.0% Oral Iron 61.8%(p<0.0001) (95% CI: 12.2, 28.3) **Secondary:** **Hb 12 g/dL** FCM 72.8%. Oral Iron 49.8%(p<0.0001) (95% CI: 14.3, 31.7) **Hb increase ≥3 g/dL** FCM 53.1% Oral Iron 35.6%(p<0.0001) (95% CI: 8.5, 26.5)

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Eight trials were conducted in other patient populations. Two of the studies were conducted in hemodialysis subjects, 2 were conducted in subjects with gastrointestinal disorders, 1 short-term study with a long-term extension was conducted in nondialysis dependent chronic kidney disease (NDD-CKD) subjects, 1 study was conducted in subjects with chronic heart failure, and 1 was conducted in subjects with a variety of etiologies of IDA. Four of the studies were controlled, 3 were uncontrolled, and 1 was a placebo-controlled, crossover safety study. The study designs, numbers of subjects exposed, the study drug doses, and a brief presentation of the results are presented for each study conducted for FCM in other IDA populations in **Table 5**.

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Table 5. Summary of Clinical Studies of FCM in Other IDA Populations

Study/ Center(s)/ # of Subjects	Design	Diagnosis and Criteria for Inclusion	Test Product Dosage Regimen Route of Administration and Duration of Treatment	Reference Therapy Route of Administration Duration of Treatment	Key Efficacy Results
Hemodialysis-Associated Anemia					
CL-15 39 sites in Belgium, and Eastern Europe Subjects: FCM:119 Iron Sucrose:118	Multicenter, open-label, randomized, active-controlled, multiple-dose study	Adult male or female subjects between the ages of 18 and 80 years (inclusive) requiring hemodialysis with iron deficiency secondary to chronic renal failure.	FCM dosage was based on the calculated iron deficit. A maximum of 200 mg iron as IV FCM was given during scheduled HD sessions (2-3 sessions/week) until the calculated cumulative dose was reached.	Iron sucrose dosage was based on the calculated iron deficit.[a] A maximum of 200 mg iron as IV iron sucrose was given during scheduled HD sessions (2-3 sessions/week) until the calculated cumulative dose was reached.	The percentage of patients reaching an increase in Hemoglobin ≥1.0 g/dL at 4 weeks after baseline. FCM 46.4% Iron Sucrose 37.2% Descriptive Statistics chi-square (p = 0.2101)

Hemodialysis-Associated Anemia					
VIT-53214 24 sites in South Africa, Romania, and Lithuania Subjects FCM:162 [One subject included in the Safety Population of the CSR was excluded from the Safety Population of the ISS as the subject never received study drug.]	Multicenter, open-label, multiple dose, uncontrolled study	Male and female patients 18-65 years of age, inclusive, with haemodialysis-associated anemia undergoing maintenance haemodialysis	FCM dosage was based on the calculated iron deficit. A maximum of 200 mg iron as IV FCM was given during scheduled HD sessions (2-3 sessions/week) until the calculated cumulative dose was reached or a maximum of 2,400 mg had been administered.	None	The percentage of patients reaching an increase in Hemoglobin ≥1.0 g/dL at any time FCM 61.7%

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Table 5. Summary of Clinical Studies of FCM in Other IDA Populations (continued)

Study/ Center(s)/ # of Subjects	Design	Diagnosis and Criteria for Inclusion	Test Product Dosage Regimen Route of Administration and Duration of Treatment	Reference Therapy Route of Administration Duration of Treatment	Key Efficacy Results
Gastrointestinal Disorder-Associated Anemia					
CL-03 8 sites in Lithuania and Russia Subjects: FCM:46	Multicenter, multiple-dose open-label, uncontrolled	Males and females between 18 and 60 years of age, inclusive, with moderate stable iron-deficiency anemia secondary to a gastrointestinal disorder and a calculated total iron requirement ≥1000 mg; ≥50% of patients in each cohort were to require ≥1500 mg total iron. Patients could be outpatients or inpatients.	IV FCM was given as either 500 mg (Cohort 1) or 1000 mg (Cohort 2) at weekly intervals for up to 4 weeks (500 mg) or 2 weeks (1000 mg) until calculated cumulative dose was reached or a maximum of 2,000 mg had been administered. The last dose could have been less, depending on the calculated total iron requirement.	None	**Percentage of patients reaching an increase in Hemoglobin ≥2.0 g/dL at 4 weeks after baseline** Cohort 1 75% Cohort 2 73%
Gastrointestinal Disorder-Associated Anemia					
CL-08 36 sites in Argentina, Austria, Belgium, Bulgaria, Mexico, Poland, Russia, and Ukraine Subjects: FCM: 137 Ferrous Sulfate: 63	Multicenter, multiple-dose randomized, open-label, active-controlled	Males and females aged 18-80 years, inclusive with iron-deficiency anemia secondary to chronic inflammatory bowel disease (ulcerative colitis or Crohn's disease) and a calculated total iron requirement of at least 1000 mg total iron.	FCM dosage was based on the calculated iron deficit. FCM was dosed same as described for Study VIT-09.	Oral iron, 100 mg iron as ferrous sulfate BID for 12 weeks	**Non-inferiority Study** **Mean change from baseline to Week 12 in Hemoglobin** FCM 3.83 g/dl Oral Iron 3.75 g/dl Lower bound of 95% CI was -0.5 g/dL with non-inferiority bound of –0.5 g/dL

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Table 5. Summary of Clinical Studies of FCM in Other IDA Populations (continued)

Study/ Center(s)/ # of Subjects	Design	Diagnosis and Criteria for Inclusion	Test Product Dosage Regimen Route of Administration and Duration of Treatment	Reference Therapy Route of Administration Duration of Treatment	Key Efficacy Results
Non-Dialysis Dependent Chronic Kidney Disease					
VIT-04 47 sites in the US, Canada, Australia, Hong Kong, Singapore, and Thailand Subjects: FCM:147 Oral Iron: 103	Multicenter, open-label, randomized, active-controlled	Male or female NDD-CKD subjects ≥ 12 years of age, GFR ≤ 45 mL/min/1.73m^2 based on the initial Baseline 1 Visit creatinine result, the average of 2 consecutive baseline central laboratory hemoglobin results drawn on different days within a 7-day period must have been ≤ 11g/dL, and the difference between the 2 hemoglobin results must have been ≤ 0.7 g/dL.	**Day 0:** maximum dose of 1,000 mg of IV FCM (15 mg/kg for weight ≤ 66 kg). **Day 17 ± 1:** maximum dose of 500 mg of IV FCM (15 mg/kg to a maximum of 500 mg) if TSAT was <30% and ferritin was <500 ng/mL . **Day 31 ± 1:** maximum dose of 500 mg of IV FCM (15 mg/kg to a maximum of 500 mg) if TSAT was <30% and ferritin was <500 ng/mL.	Oral iron, 65 mg iron as ferrous sulfate TID for 8 weeks	**Primary:** Hb increase ≥1 g/dL 60.4% FCM vs. 34.7% Oral Iron (p<0.0001) (95% CI: 13.0, 38.5)
Non-Dialysis Dependent Chronic Kidney Disease					
VIT-05 28 investigative sites in the US, Canada, and Australia 127 subjects	Long term extension study of VIT-04	Subjects who completed the VIT04 study through Day 56 or subjects who were discontinued from VIT04 for requiring intervention with an increase in dose of EPO, the addition of EPO, or the use of iron outside the protocol.	Laboratory evaluations were performed every 28 days. For a TSAT <25% and ferritin <300 ng/mL: maximum dose of 1,000 mg of FCM (15 mg/kg for weight ≤ 66 kg) IV was administered within 7 days of the qualifying visit. If subject did not qualify for the 1,000 mg FCM dose but their TSAT was <30% and ferritin was <500 ng/mL: maximum dose of 500 mg of FCM (15 mg/kg to a maximum of 500 mg) IV was administered within 7 days of the qualifying visit.	None	**Safety Study** No primary efficacy endpoint.

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Table 5. Summary of Clinical Studies of FCM in Other IDA Populations (continued)

Study/ Center(s)/ # of Subjects	Design	Diagnosis and Criteria for Inclusion	Test Product Dosage Regimen Route of Administration and Duration of Treatment	Reference Therapy Route of Administration Duration of Treatment	Key Efficacy Results
Iron Deficiency Anemia					
VIT-06 62 sites in US, Australia, and Mexico 594 subjects	Multicenter, single-dose, blinded, randomized, placebo-controlled crossover, safety study	Males / females, ≥18 years of age, with a Hg ≤12 g/dL, TSAT ≤25%, and ferritin <300 ng/mL (IDA due to HD or NDD-CKDor inflammatory bowel disease), or ferritin ≤100 ng/mL (iron-deficiency anemia due to other conditions)	A maximum single dose of IV FCM ≤1000 mg (15 mg/kg for weight ≤66 kg).	Placebo (Crossover Study: Subjects received a single dose of either FCM or placebo on Day 0. Following a 7-day washout period, subjects crossed over to receive a single dose of the treatment opposite of that received on Day 0.)	Safety Study
Chronic Heart Failure					
FER-CARS-01 14 sites in Russia Subjects: FCM: 30 Iron Sucrose: 27 Control: 15	Multicenter, blinded, randomized, controlled, parallel group	Male or female subjects, ≥18 years of age, NYHA II-IV class, stable symptomatic CHF, GFR < 60 mL/min, Hemoglobin < 14.5 g/dL and > 10 g/dL, ferritin < 100 mg/L or 100 - 300 mg/L with TSAT < 20% or hypochromic red cells > 10%, normal electrolyte, red cell folate, vitamin B12 status, resting blood pressure ≤ 160/100 mmHg	FCM dosage was based on the calculated iron deficit.[a] Correction phase: A maximum of 200 mg iron as IV FCM was given weekly until calculated iron dose was reached. In the control group, the number of normal saline injections corresponded to the calculated total dose. Maintenance phase: 200 mg IV FCM in the treatment groups/5 mL normal saline in the control group every 4 weeks.	Iron sucrose dosage was based on the calculated iron deficit.[a] Correction phase: A maximum of 200 mg iron as IV iron sucrose was given weekly until calculated iron dose was reached. In the control group, the number of normal saline injections corresponded to the calculated total dose. Maintenance phase: 200 mg IV iron sucrose in the treatment groups/5 mL normal saline in the control group every 4 weeks.	Pitol Study Hemoglobin results Not available.

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Two additional studies of FCM are ongoing assessing the safety and tolerability of FCM compared to standard medical care in the treatment of HUB and postpartum patients (VIT-17) and in the treatment of CKD patients (VIT-18). The study designs, numbers of subjects exposed to date, the study drug doses, and the criteria for evaluation are presented for each ongoing study in **Table 6**.

As of December 27, 2007, 141 subjects have been treated in these 2 ongoing studies and no serious adverse events (including deaths) or significant safety issues have been identified.

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Table 6. Summary of Ongoing Clinical Studies of FCM

Study/ Center(s)/ # of Subjects	Design	Diagnosis and Criteria for Inclusion	Test Product Dosage Regimen Route of Administration and Duration of Treatment	Reference Therapy Dose Regimen Route of Administration and Duration of Treatment	Current Enrollment As of 12/27/07
Postpartum and Heavy Uterine Bleeding Anemia					
VIT-17 100 Sites planned in the US **Planned Enrollment** FCM: 500 female subjects Standard Medical Care: 500 female subjects	Open-label, multicenter, randomized, single-dose, active-control study	Postpartum: Screening Visit Hemoglobin ≤11 g.dL obtained ≥18 hours post-delivery. Heavy uterine bleeding: Hemoglobin ≤11.5 g.dL and Screening Visit central laboratory Hemoglobin ≤11.5 g.dL	Undiluted dose of iron as FCM (15 mg/kg up to a maximum of 1000mg) over 15 minutes as a slow intravenous injection on Day 0. Pre-pregnancy weight used if subject is postpartum.	Standard medical care for the treatment of the subject's iron deficiency anemia as determined by the Investigator from Day 0 to Day 30.	Sites: 41 Subjects: Screened: 176 Randomized: 104 Completed: 27 Discontinued: 3
Non Dialysis-Dependent and Dialysis-Dependent Chronic Kidney Disease Anemia					
VIT-18 100 Sites planned in the US **Planned Enrollment** FCM: 250 subjects Standard Medical Care: 250 subjects	Open-label, multicenter, randomized, single dose, active-control, study	NDD-CKD: ≥3 month history Hb <11.5 g/dL, TSAT <25%, and Ferritin <300 ng/mL. HD-CKD: ≥6 month history of haemodialysis. Hb <12 g/dL,, TSAT <30%, and Ferritin <500 ng/mL.	**NDD-CKD**: An undiluted dose of iron as FCM intravenously (15mg/kg up to a maximum of 1000 mg) over 15 minutes as a slow intravenous injection on Day 0. **HD-CKD:** 200 mg of FCM intravenous push undiluted directly into the venous line of the dialyzer on Day 0.	Standard medical care for the treatment of the subject's iron deficiency anemia as determined by the Investigator.	Sites: 21 Subjects: Screened: 77 Randomized: 37 Completed: 11 Discontinued: 0

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2.4 Dose

2.4.1 Oral Iron

The dose of oral iron used as an active control represents the full therapeutic dose and standard of care for IDA; 195 mg to 200 mg of elemental iron/day given as ferrous sulfate.[52] Other oral iron products were considered. These products were not utilized due to reduced bioavailability and/or lower elemental iron content.

2.4.2 FCM

FCM is administered intravenously as a maximum single dose of 15 mg/kg of iron up to 1000 mg over 15 minutes. The safety of this maximum single dose is supported by pre-clinical and in vitro testing, pharmacokinetic and pharmacodynamic findings, the lack of a relationship with the incidence of serious and non-serious adverse events, including mortality and compares favorably with the safety of administration of much lower individual doses of available intravenous iron agents. This dose is further supported by the medical need for rapid, efficient delivery of iron in postpartum and heavy uterine bleeding patients requiring rapid, effective correction of their iron deficiency anemia. Single doses of this size are not novel; iron dextran is used off label in the US (labeled outside the US) when rapid/efficient iron repletion is clinically required using single doses exceeding 1000 mg. For example, the approved label for Infufer®, an iron dextran injection product marketed in Canada, would allow for a dose of 2000 mg of iron dextran for a 70 kg patient with a hemoglobin of 8 g/dL over 1-3 hours. Iron dextran is a stable drug complex like FCM, allowing for administration of a large single dose. However, documented anaphylaxis and related delayed hypersensitivity reactions has limited the use of higher doses of iron dextran Neither of these safety issues have been observed with FCM.

A full pre-clinical safety program was conducted in iron replete animals supporting the 15 mg/kg FCM single dose. The maximum non-lethal dose of FCM in rats was 1000 mg/kg and the LD_{50} was greater than 2000 mg/kg. The maximum lethal dose is approximately 5 times that of iron sucrose. Safety pharmacology studies showed no effects on cardiac, respiratory, nervous, or renal systems at doses up to 90 mg/kg. Acute and chronic toxicology studies were also conducted and were also supportive of the 15mg/kg single FCM dose as well as the 2500 mg total FCM dose.

In vitro studies were consistent with the findings in clinical trials that the iron in ferric carboxymaltose is tightly bound to the carbohydrate, limiting risk associated with release of biologically active iron. Dialysable free iron has not been detected with ferric carboxymaltose[53] and the iron in ferric carboxymaltose does not participate in direct donation to transferrin[54] (the risk for bioactive iron reactions may correlate with the percent iron donation to transferrin).

Pharmacokinetic studies supports the appropriateness of this dosing regimen, documenting the lack of total serum iron accumulation, total serum iron returns to baseline within 7 days after the first and second infusion of 1000 mg of FCM. Two studies were performed to assess the pharmacokinetic/pharmacodynamic profile of FCM. In adults with mild IDA treated with placebo or intravenous doses of 100, 500, 800 or 1,000 mg over 15 minutes (Study CL-02), FCM was well tolerated at all doses. Adverse events possibly related to study drug were infrequent and not dose related. Neither safety laboratory values nor vitals signs or ECGs revealed any clinically

significant change in comparison to placebo. The iron elimination component of FCM was essentially mono-exponential with an elimination half-life of 9.6 h, total clearance of 2.7 mL/min, total serum iron maximum concentration of 333 μg/mL, and time to maximum concentration of 1.2 hours after end of the infusion. The steady state apparent volume of distribution averaged 2.6 L. There was negligible renal elimination.

The percent transferrin saturation (serum iron/total iron binding capacity) was demonstrated to not be useful in guiding dose selection. The rise in TSAT seen early after dosing was independent of administered dose over the 100-1000mg dose range. While the IV iron complex is in the serum early after administration, measurements of TSAT are not valid as the assays for serum iron measure both the iron in the serum and part of the iron in the drug complex.[55] The appropriateness of the 1000 mg is supported by the finding in the Phase 2/3 clinical trials that following the 1,000 mg dose TSAT was within normal range at Day 7 and were no higher than those seen after administration of 500 mg of either FCM or iron sucrose. The TSAT following FCM dosing was lower than the values achieved with oral iron in the heavy uterine bleeding clinical trials.

The formula used to calculate total iron dose to correct IDA is the same for all intravenous iron agents, reflecting the assumption that core iron chemistry and treatment efficacy, gauged by dose of elemental iron administered, are equivalent. The total amount of intravenous iron (in mg) needed to correct anemia and replete tissue iron stores was calculated in the FCM clinical trials by the Ganzoni formula[56] modified to include adjustment for baseline iron status:

weight in kg x (15 – baseline hemoglobin) x 2.4 + 500.

Fifteen (15) is the target hemoglobin in g/dL, 2.4 is a unit-less conversion constant and 500 is the target iron stores in mg and only included if TSAT <20% or ferritin <50 ng/mL.

This formula is generally considered conservative and may under estimate iron need.

Dose limitations, risk of anaphylaxis or bioactive iron reactions render current intravenous iron agents impractical or unsafe for this patient population. Given the total iron needed to correct IDA and replenish iron stores, dose limits of available intravenous iron agents pose formidable barriers to use in the treatment of most patients with IDA.

The average total iron doses required in the FCM trials exceeded 1500 mg in women with postpartum anemia (Studies VIT-11 and VIT-01) and 1600 mg in women with anemia and HUB (Study VIT-02/VIT-03). Thus, to be treated with currently available intravenous iron agents, the average patient with IDA, as described in the Luitpold-sponsored studies, would require an initial test dose followed by up to 16 doses of iron dextran (as labeled in the US), each accompanied by personnel equipped and trained for resuscitation of anaphylaxis; 13 doses of ferric gluconate; 8 doses of iron sucrose by intravenous injection; or 4 doses of iron sucrose by prolonged (2.5 hours) intravenous infusion **(Table 2).** Only iron dextran, which carries a Black Box warning is approved for use in the target population for approval (postpartum/HUB). By contrast, choice of the FCM dose of 15 mg/kg up to a maximum of 1000 mg permits correction of anemia and replenishment of iron stores in 1-2 doses in approximately 92% of postpartum and HUB patients, yet avoids reactions characteristic of either allergic hypersensitivity or bioactive iron reaction.

The risk of anaphylaxis is related to the carbohydrate ligand (dextran and its derivatives), and is independent of rate or dose of administration. Intravenous iron agents share similar core iron chemistry but differ by core size, particle size, carbohydrate composition and strength of the carbohydrate-core iron bond. The risk of a bioactive iron reaction is related to particle chemistry, particle size, and the dose and rate of intravenous iron infusion. Bioactive iron reactions are characterized by hypotension, pain in the flank, abdomen or chest, and nausea, vomiting or diarrhea. Bioactive iron reactions are dose-limiting for both rapid intravenous injection and prolonged intravenous infusion.

2.4.3 Exposure to FCM in Clinical Trials

The extent of exposure to FCM during the entire trial program excluding the extension study (VIT-05) is presented in **Table 7**. Among the 1998 subjects, from all populations, treated with FCM in 11 of the 12 multicenter studies, the number of infusions received ranged from 1 to 11; however, the majority of the subjects received only 1 (36.2%) or 2 (43.1%) doses of FCM. The mean total dose of FCM received was 1270.1 (± 371.65) mg and the mean maximum single dose received was 811.2 (± 287.61) mg. The maximum single FCM dose received by the majority of the subjects (51.30%) was 1000 mg.

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Table 7. Summary of Extent of Exposure to FCM (All Multicenter Studies Excluding Extension Study)

	FCM (N=1998)
Number of Infusions	
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	
Mean (SD)	1270.1 (371.65)
Median	1200
Minimum[a] – Maximum	0.0-3400.0
0 to 1000 mg	810 (40.54%)
1001 to 1400 mg	622 (31.13%)
>1400 mg	566 (28.33%)
Maximum Single Dose (mg)	
Mean (SD)	811.2 (287.61)
Median	1000
Minimum[a] – Maximum	0.0-1000.0
0-399 mg	319 (15.97%)
400-499 mg	1 (0.05%)
500-599 mg	25 (1.25%)
600-799 mg	157 (7.86%)
800-999 mg	471 (23.57%)
1000 mg	1025 (51.30%)

Includes Studies VIT-11. VIT-01, VIT-09, VIT-02/VIT-03, CL-03, CL-08, VIT-04, CL-15, VIT-53214, VIT-06, and CARS
SD = Standard Deviation
a Three subjects had data entered for the start and stop times of the infusion but no data for the actual amount of drug infused. These 3 subjects with unspecified doses are listed under the "1" infusion category and total dose is indicated as 0.

The remaining study (Study VIT-05) was a 44-week extension study to Study VIT-04 and data for this trial are presented separately from the other 11 multicenter trials (**Table 8**). In Study VIT-05, the mean number of doses received during the study was 3.0 (± 1.44) for ESA users and 2.3 (± 1.52) for non-ESA users. The average days between doses was 71.2 (± 38.16) for ESA users and 85.1 (± 44.57) for non-ESA users. The mean milligram (± SD) exposure during the study, calculated as the total dose of study drug administered, was 1791.4 (± 858.99) mg for ESA users and 1459.6 (± 991.04) mg for non-ESA users.

Table 8. Summary of Extent of Exposure (Extension Study VIT-05)

	ESA Users	Non-ESA Users	Total
Number of Doses			
N	62	65	127
Mean (SD)	3.0 (1.44)	2.3 (1.52)	2.6 (1.51)
Median	3	2	2
Minimum – Maximum	1 – 6	1 - 8	1 - 8
Average Days Between Doses			
N	54	43	97
Mean (SD)	71.2 (38.16)	85.1 (44.57)	77.4 (41.49)
Median	64	77	69
Minimum – Maximum	26 - 237	28 - 224	26 - 237
Total FCM Dose			
N	62	65	127
Mean (SD)	1791.4 (858.99)	1459.6 (991.04)	1621.6 (940.12)
Median	1500	1000	1500
Minimum – Maximum	500 - 4000	175 - 5500	175 - 5500

SD = Standard Deviation

The extent of exposure to FCM among postpartum and HUB subjects during the trial program is presented in **Table 9**. Among the 1052 postpartum and HUB subjects treated with FCM, the number of infusions received ranged from 1 to 3, with the majority (93.8%) of the subjects receiving 1 or 2 doses of FCM. The mean total dose of FCM received was 1331.1 (± 385.14) mg and the mean maximum single dose received was 923.6 (± 123.31) mg. The maximum single FCM dose received by the majority of the subjects (59.51%) was 1000 mg.

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Table 9. Summary of Extent of Exposure to FCM (All Postpartum and HUB Study Subjects)

	FCM (N=1052)
Number of Infusions	
1[a]	317 (30.1%)
2	670 (63.7%)
3	65 (6.2%)
Total Dose of Iron (mg) Received	
Mean (SD)	1331.1 (385.14)
Median	1300
Minimum[a] – Maximum	0.0-2500.0
0 to 1000 mg	347 (32.98%)
1001 to 1400 mg	359 (34.13%)
>1400 mg	346 (32.89%)
Maximum Single Dose (mg)	
Mean (SD)	923.6 (123.31)
Median	1000
Minimum[a] – Maximum	0.0-1000.0
0-399 mg	6 (0.57%)
400-499 mg	0
500-599 mg	2 (0.19%)
600-799 mg	101 (9.60%)
800-999 mg	317 (30.13%)
1000 mg	626 (59.51%)

Includes Studies VIT-11, VIT-01, VIT-09, VIT-02/VIT-03, and VIT-06
SD = Standard Deviation
a Two subjects had data entered for the start and stop times of the infusion but no data for the actual amount of drug infused. These 2 subjects with unspecified doses are listed under the "1" infusion category and total dose is indicated as 0.

2.5 Efficacy in Postpartum and Heavy Uterine Bleeding (HUB) Patients

The efficacy of FCM for the treatment of IDA was consistently demonstrated across studies of varying IDA etiologies. As previously stated, Luitpold decided to focus on the need identified for a product of this type in the postpartum and HUB populations. The postpartum and HUB studies were the most rigorous and comprehensive trials conducted in the overall FCM program. This document will focus on randomized, controlled parallel-group studies that were conducted in the postpartum and HUB populations (Studies VIT-11, VIT-01, VIT-09 and VIT-02/VIT-03).

Each of these efficacy trials utilized an open-label design due to the differences in study drug administration (intravenous FCM versus oral iron) and the difficulty in blinding the intravenous iron product (dark color). As the study endpoints were based on objective laboratory values, it was determined that the open-label design would not result in any potential bias in the interpretation of results. All efficacy analyses were prespecified in the statistical analysis plans prior to database lock.

Three of the studies were conducted by Luitpold (VIT-11, VIT-01, and VIT-02/VIT-03) with generally similar key endpoints including the proportion of subjects who achieved a hemoglobin

>12 g/dL and the proportion of subjects who achieved an increase in hemoglobin of ≥2 g/dL and ≥3 g/dL. Endpoint analyses were performed using the Intent-to-Treat, Modified Intent-to-Treat, and Evaluable Populations. Across the Luitpold-sponsored studies, definitions of these populations were generally consistent, as all randomized subjects regardless of receipt of study drug were included in the Intent-to-Treat Population and all subjects with documented anemia who had received at least 1 dose of study drug and had a post-baseline assessment were included in the Modified Intent-to-Treat population. Subjects in the Modified Intent-to-Treat Population who received at least 67% of required study drug, were followed until Day 42, and had no major protocol violations were included in the Evaluable Population.

Key efficacy endpoints for each of the studies that were conducted by Luitpold are presented for the Intent-to-Treat and Modified Intent-to-Treat populations in **Table 10**.

Table 10. Summary of Key Efficacy Endpoints from Randomized, Controlled, Parallel-Group Studies Sponsored by Luitpold in Postpartum and HUB Populations (Intent-to-Treat and Modified Intent-to-Treat Populations)

Efficacy Endpoint Achieved Anytime During Study	Number (%) Subjects		Fisher's Exact p-value	95% CI
	FCM n/N (%)	Oral Iron n/N (%)		
Intent-to-Treat Population				
Study VIT-11				
Hb >12 g/dL*	127/143 (88.8%)	98/148 (66.2%)	<0.0001	12.97, 32.22
Increase from BL in Hb ≥3 g/dL	127/143 (88.8%)	95/148 (64.2%)	<0.0001	15.33, 33.92
Study VIT-01				
Increase from BL in Hb ≥2 g/dL*	162/182 (89.0%)	159/179 (88.8%)	non-inferiority trial	-6.29, 6.66
Hb >12 g/dL	152/182 (83.5%)	116/179 (64.8%)	<0.0001	9.88, 27.54
Increase from BL in Hb ≥3 g/dL	145/182 (79.7%)	102/179 (57.0%)	<0.0001	13.37, 32.00
Study VIT-02/VIT-03				
Increase from BL in Hb ≥2 g/dL*	187/246 (76.0%)	139/231 (60.2%)	0.0002	7.58, 24.11
Hb >12 g/dL	166/246 (67.5%)	112/231 (48.5%)	<0.0001	10.29, 27.70
Increase from BL in Hb ≥3 g/dL	121/246 (49.2%)	80//231 (34.6%)	0.0016	5.80, 23.31
Modified Intent-to-Treat Population				
Study VIT-11				
Hb >12 g/dL*	127/139 (91.4%)	98/147 (66.7%)	<0.0001	15.20, 34.20
Increase from BL in Hb ≥3 g/dL	127/139 (91.4%)	95/147 (64.6%)	<0.0001	17.08, 36.41
Study VIT-01				
Increase from BL in Hb ≥2 g/dL*	162/168 (96.4%)	159/169 (94.1%)	non-inferiority trial	-2.19, 6.88
Hb >12 g/dL	152/168 (90.5%)	116/169 (68.6%)	<0.0001	13.55, 30.12
Increase from BL in Hb ≥3 g/dL	145/168 (86.3%)	102/169 (60.4%)	<0.0001	16.93, 34.98
Study VIT-02/VIT-03				
Increase from BL in Hb ≥2 g/dL*	187/228 (82.0%)	139/225 (61.8%)	<0.001	12.2, 28.3
Hb >12 g/dL	166/228 (72.8%)	112/225 (49.8%)	<0.001	14.3, 31.7
Increase from BL in Hb ≥3 g/dL	121/228 (53.1%)	80//225 (35.6%)	<0.001	8.5, 26.5

* Primary endpoint
n = number of subjects who achieved endpoint, N = number of subjects in group, % = n divided by N
CI = confidence interval based on normal approximation to the binomial

For the primary efficacy endpoint in each study, the superiority of FCM to oral iron was first demonstrated statististically at Day 7 (VIT-01 and VIT-02/VIT-03) or Day 14 (VIT-11; **Table 11**).

Table 11. Summary of the Proportion of Subjects Who Achieved the Primary Efficacy Endpoint of the Studies on or Before Each Visit During the Study from Randomized, Controlled, Parallel-Group Studies Sponsored by Luitpold in Postpartum and HUB Populations (Modified Intent-to-Treat Populations)

Day	FCM n/N (%)		Oral Iron n/N (%)		Fisher's Exact p-value	
	LOCF	OC	LOCF	OC	LOCF	OC
VIT-11: Hb >12 g/dL on or before reference day						
7	23/139 (16.5%)	23/138 (16.7%)	20/147 (13.6%)	20/147 (13.6%)	0.5118	0.5104
14	78/139 (56.1%)	78/138 (56.5%)	46/147 (31.3%)	43/144 (29.9%)	<0.0001	<0.0001
28	111/139 (79.9%)	106/138 (76.8%)	80/147 (54.4%)	70/145 (48.3%)	<0.0001	<0.0001
42	127/139 (91.4%)	117/137 (85.4%)	98/147 (66.7%)	83/143 (58.0%)	<0.0001	<0.0001
VIT-01: Increase in Hb ≥2 g/dL on or before reference day						
7	98/168 (58.3%)	98/168 (58.3%)	65/169 (38.5%)	65/164 (39.6%)	0.0003	0.0007
14	147/168 (87.5%)	144/167 (86.2%)	122/169 (72.2%)	111/162 (68.5%)	0.0006	0.0001
28	160/168 (95.2%)	153/163 (93.9%)	151/169 (89.3%)	139/163 (85.3%)	0.0644	0.0174
42	162/168 (96.4%)	151/163 (92.6%)	159/169 (94.1%)	143/161 (88.8%)	0.4433	0.2556
VIT-02/VIT-03: Increase in Hb ≥2 g/dL on or before reference day						
7	15/219 (6.8%)	15/219 (6.8%)	6/222 (2.7%)	6/222 (2.7%)	0.046	0.046
14	87/228 (38.2%)	85/219 (38.8%)	59/225 (26.2%)	56/218 (25.7%)	0.007	0.004
28	155/228 (68.0%)	147/215 (68.4%)	109/225 (48.4%)	102/215 (47.4%)	<0.001	<0.001
42	187/228 (82.0%)	163/212 (76.9%)	139/225 (61.8%)	120/209 (57.4%)	<0.001	<0.001

n = number of subjects who achieved endpoint, N = number of subjects in group, % = 100 x (n divided by N), LOCF = last observation carried forward, OC = observed cases

The remaining study (VIT-09) was conducted by a European partner with a primary endpoint of mean change from baseline in hemoglobin. Results of this trial are presented in Section 2.5.3.

Outlines of the studies were previously presented in **Table 4**. Efficacy results are presented for each of the 4 studies individually in Sections 2.5.1 through 2.5.4.

2.5.1 Luitpold-Sponsored Study VIT-11: The Safety and Efficacy of a Hematinic Agent in the Treatment of Postpartum Patients

Study Objectives and Endpoints

Study VIT-11 was an open-label, Phase 3, randomized, active-controlled trial. The primary objective of this study was to evaluate the efficacy of intravenous FCM in comparison with oral iron in improving hemoglobin in postpartum anemia. The secondary objective of this study was to evaluate the safety and tolerability of intravenous FCM in comparison with oral iron in postpartum anemia.

The primary measure of efficacy was achieving a hemoglobin >12 g/dL anytime between baseline and end of study or time of intervention.

Major secondary endpoints in ranked order of testing included:

- Proportion of subjects with an increase in hemoglobin ≥3 g/dL anytime between baseline and end of study or time of intervention.
- Proportion of subjects who achieved a hemoglobin >12 g/dL on or before Day 42, Day 28, and Day 14. Two summaries were provided. The primary summary was based on the last observation carried forward method in which subjects who discontinued from the study prior to Day 42 were evaluated based on their last non-missing post baseline visit. The secondary summary was based on the observed cases method.
- Proportion of subjects who had an increase in hemoglobin ≥3 g/dL on or before Day 42, Day 28, and Day 14. Two summaries were provided. The primary summary was based on the last observation carried forward method in which subjects who discontinued from the study prior to Day 42 were evaluated based on their last non-missing post baseline visit. The secondary summary was based on the observed cases method.
- Time to achieving a hemoglobin >12 g/dL.

The Modified Intent-to-Treat population was the primary population for evaluating all efficacy endpoints. The Intent-to-Treat and Evaluable populations were included as supportive analyses.

Main Inclusion Criteria and Study Design

Postpartum subjects within 10 days after delivery with hemoglobin ≤10 g/dL at Baseline based on the average of 2 hemoglobin values drawn 12 hours apart and ≥18 hours postpartum, who met all inclusion/exclusion criteria, and had given informed consent, were randomized. The duration of the study for each subject was a maximum of 8 weeks. Within 10 days post-delivery, subjects meeting the entrance criteria were randomized via an interactive voice response system (IVRS) into the treatment phase and received their first dose of study drug.

At randomization, subjects were stratified by hemoglobin levels (9.1-10.0 g/dL, 8.1-9.0 g/dL, ≤8.0 g/dL), requirement for cesarean section (C-section), and screening iron indices (ferritin ≤25 ng/mL, ferritin >25 ng/mL). Subjects were randomly assigned to either FCM (up to a maximum cumulative iron dose of 2,500 mg administered intravenously based on iron-deficit calculations; the calculated dose was given in divided doses of up to 1,000 mg weekly) or oral iron (325 mg of ferrous sulfate 3 times daily [TID] x 6 weeks). The administration of the initial dose of study drug could have occurred either during their inpatient stay or after discharge. Assessments for efficacy (hematologic parameters and iron indices) and safety (adverse events and laboratory results) were performed on post-randomization Days 7, 14, 28, and 42.

Disposition

Two hundred ninety-one (291) subjects were randomized at 28 centers to receive FCM (143 subjects) or oral iron (148 subjects). Of these 291 subjects, 1 who was randomized to FCM and 1 who was randomized to oral iron were discontinued from the study prior to dosing due to subject request. Therefore, a total of 142 subjects were treated in the FCM group and 147 subjects were treated in the oral iron group (**Table 12**).

One hundred thirty-eight (138; 97.2%) of the 142 subjects in the FCM group and 144 (98.0%) of the 147 subjects in the oral iron group completed the study. Of the 4 subjects in the FCM group who did not complete the study, 3 were lost to follow-up and 1 had an intervention and received a

blood transfusion. Of the 3 subjects in the oral iron group who did not complete the study, 1 was lost to follow-up, 1 discontinued due to subject request, and 1 had an intervention and received a blood transfusion.

Table 12. Subject Disposition and Study Termination During the Treatment Phase (Study VIT-11)

	FCM	Oral Iron	Total
All Randomized Subjects	143	148	291
Treated Subjects	142 (100%)	147 (100%)	289 (100%)
Subjects Discontinued From Study	4 (2.8%)	3 (2.0%)	7 (2.4%)
Subject had intervention			
Received blood transfusion	1 (0.7%)	1 (0.7%)	
Did not complete study per protocol			
Lost to follow-up	3 (2.1%)	1 (0.7%)	
Subject request	0	1 (0.7%)	
Subjects Who Completed Study	138 (97.2%)	144 (98.0%)	282 (97.6%)

Demographic and Baseline Characteristics

No statistically significant differences were observed between the treatment groups among all treated subjects for demographic characteristics (**Table 13**).

Baseline characteristics of mean hemoglobin, TSAT, and ferritin values at baseline were similar between the FCM (8.89 g/dL, 9.44%, and 24.05 ng/mL, respectively) and oral iron (8.88 g/dL, 9.35%, 23.91 ng/mL, respectively) treatment groups. The proportion of subjects with a baseline hemoglobin ≤8.0 g/dL at randomization was 14.1% in the FCM group and 14.3% in the oral iron group. The majority of the subjects in both treatment groups had received previous iron therapy (FCM: 80.3%; oral iron: 78.9%). Fourteen subjects (6 FCM and 8 oral iron) had a prior history of iron intolerance.

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Table 13. Demographic and Baseline Characteristics (Study VIT-11: All Treated Subjects)

	FCM (N=142)	Oral Iron (N=147)	p-value
Demographic Characteristic			
Age (years)			
Mean (SD)	26.43 (6.02)	26.49 (5.55)	0.932
Median	25.40	26.32	
Minimum – Maximum	16.79 – 43.16	15.76 – 43.41	
<19	14 (9.9%)	7 (4.8%)	0.115
≥19	128 (90.1%)	140 (95.2%)	
Race			0.162
Caucasian	104 (73.2%)	96 (65.3%)	
Hispanic	15 (10.6%)	20 (13.6%)	
African American	22 (15.5%)	27 (18.4%)	
Asian	0	3 (2.0%)	
Other	1 (0.7%)	1 (0.7%)	
Baseline Characteristic			
Baseline Hemoglobin (g/dL)			0.941
Mean (SD)	8.89 (0.90)	8.88 (0.89)	
Median	9.13	9.10	
Minimum – Maximum	5.65 – 10.35	6.10 – 10.50	
Baseline TSAT (%)			0.871
Mean (SD)	9.44 (4.65)	9.35 (4.71)	
Median	8.00	8.00	
Minimum – Maximum	2.00 – 26.00	2.00 – 28.00	
Baseline Ferritin (ng/mL)			0.949
Mean (SD)	24.05 (18.52)	23.91 (16.34)	
Median	19.80	19.20	
Minimum – Maximum	4.40 – 123.90	3.70 – 91.60	
Prior Iron Intolerance			0.786
Yes	6 (4.2%)	8 (5.4%)	
Previous Iron Therapy			0.884
Yes	114 (80.3%)	116 (78.9%)	

SD=Standard Deviation

Extent of Exposure and Compliance

Among all treated subjects, the mean (± SD) exposure during the study, calculated as the total dose of study drug (elemental iron) administered, was 1503.5 (± 384.53) mg in the FCM group and 7906.1 (± 981.42) mg in the oral iron group (**Table 14**).

Table 14. Summary of Extent of Exposure (Study VIT-11: All Treated Subjects)

Total Dose of Iron (mg) Received	FCM	Oral Iron
	(N=142)	(N=147)
Mean (SD)	1503.5 (384.53)	7906.1 (981.42)
95% Confidence Interval of Mean	1439.73, 1567.31	7746.14, 8066.10
Median	1500	8190
Minimum – Maximum	400 – 2500	1170 – 9620

SD=Standard Deviation

In the Modified Intent-to-Treat Population, mean study drug usage and the proportion of subjects who used 67% of study drug were comparable between the FCM treatment group and the oral iron treatment group (**Table 15**).

Table 15. Summary of Study Drug Usage During the Treatment Phase (Study VIT-11: Modified Intent-to-Treat Population)

% Compliance	FCM	Oral Iron
	(N=139)	(N=147)
Total Iron Received (from CRF)/Total Iron Expected Based on Actual Days on Study and IVRS Data		
Mean (SD)	98.9 (6.22)	96.2 (8.84)
95% Confidence Interval of Mean	97.85, 99.94	94.78, 97.67
Median	100	99
Minimum – Maximum	50 – 100	56 – 117
Subjects ≥67% Compliant	137 (98.56%)	144 (97.96%)

Datasets Analyzed

All randomized subjects, regardless of whether or not they had received a dose of study medication, were included in the Intent-to-Treat Population (N=291; **Table 16**). Subjects in the Intent-to-Treat Population who did not have post-baseline data were treated as failures in the analysis of the primary endpoint.

All subjects who had documented postpartum anemia at baseline (characterized by the average of the 2 baseline central laboratory hemoglobin measurements being <11.0 g/dL), received at least 1 dose of study medication, and had at least 1 post-baseline hemoglobin assessment were included in the Modified Intent-to-Treat Population (N=286). All subjects in the Modified Intent-to-Treat Population who received at least 67% of required study drug, were followed until the Day 42 evaluation, and had no major protocol violations were included in the Evaluable Population (N=281).

Table 16. Datasets Analyzed (Study VIT-11)

Population	FCM	Oral Iron
Intent-to-Treat Population (All Randomized Subjects)	143	148
Modified Intent-to-Treat Population	139	147
Evaluable Population	138	143

Efficacy

The primary efficacy endpoint was the proportion of subjects who achieved a hemoglobin >12.0 g/dL at anytime during the study (i.e., between baseline and the end of study or time of

intervention). The primary efficacy analysis was the superiority of the proportion of subjects who achieved a hemoglobin >12.0 g/dL at anytime during the study for FCM relative to oral iron based on a 2-sided Fisher's exact test on the unstratified rate. The Modified Intent-to-Treat population was the primary population for evaluating all efficacy endpoints. The Intent-to-Treat and Evaluable populations were included as supportive analyses.

Although the total dose of iron received in the oral iron group was more than 5 times that received in the FCM group, the proportion of subjects in the Modified Intent-to-Treat Population who achieved a hemoglobin >12.0 g/dL was statistically significantly greater in the FCM group (91.4%) compared with the oral iron group (66.7%) and the superiority of FCM relative to oral iron was demonstrated (**Table 17**). Similar results were also observed in the Evaluable and Intent-to-Treat Populations.

Table 17. Summary of the Proportion of Subjects Who Achieved a Hemoglobin >12.0 g/dL Anytime During the Study (Study VIT-11: Modified Intent-to-Treat, Evaluable, and Intent-to-Treat Populations)

Hemoglobin >12 g/dL Anytime During Study	Number (%) Subjects		Fisher's Exact p-value	95% CI
	FCM n/N (%)	Oral Iron n/N (%)		
Modified Intent-to-Treat Population	127/139 (91.4%)	98/147 (66.7%)	<0.0001	15.20, 34.20
Evaluable Population	126/138 (91.3%)	96/143 (67.1%)	<0.0001	14.65, 33.70
Intent-to-Treat Population	127/143 (88.8%)	98/148 (66.2%)	<0.0001	12.97, 32.22

n = number of subjects who achieved a hemoglobin >12.0 g/dL at anytime during the study, N = number of subjects in group, % = n divided by N
CI = confidence interval based on normal approximation to the binomial

Greater proportions of FCM subjects compared with oral iron subjects achieved a hemoglobin >12.0 g/dL on or before each visit; differences between the treatments groups were statistically significant at Days 14, 28, and 42 (**Table 18**).

Table 18. Summary of the Proportions of Subjects Who Achieved a Hemoglobin >12.0 g/dL on or Before Each Visit During the Study (Study VIT-11: Modified Intent-to-Treat Populations)

Day	FCM n/N (%)		Oral Iron n/N (%)		Fisher's Exact p-value	
	LOCF	OC	LOCF	OC	LOCF	OC
VIT-11: Hb >12 g/dL on or before reference day						
7	23/139 (16.5%)	23/138 (16.7%)	20/147 (13.6%)	20/147 (13.6%)	0.5118	0.5104
14	78/139 (56.1%)	78/138 (56.5%)	46/147 (13.6%)	43/144 (29.9%)	<0.0001	<0.0001
28	111/139 (79.9%)	106/138 (76.8%)	80/147 (54.4%)	70/145 (48.3%)	<0.0001	<0.0001
42	127/139 (91.4%)	117/137 (85.4%)	98/147 (66.7%)	83/143 (58.0%)	<0.0001	<0.0001

n = number of subjects who achieved endpoint, N = number of subjects in group, % = 100 x (n divided by N), LOCF = last observation carried forward, OC = observed cases

FCM subjects with baseline hemoglobin concentrations ≤10.0 g/dL achieved better responses than oral iron subjects, while responses among the 15 subjects with baseline hemoglobin concentrations ≥10.1 g/dL were similar between the treatment groups. Among subjects who

achieved a hemoglobin >12.0 g/dL at anytime during the study, the largest difference between the FCM and oral iron groups was observed in subjects whose baseline hemoglobin was ≤8 g/dL (FCM: 78.9%; oral iron: 43.5%). The time to achieve a hemoglobin >12.0 g/dL was statistically significantly shorter for FCM subjects (median of 14.0 days) compared with oral iron subjects (median of 27.0 days).

The FCM group had a statistically significantly greater proportion of subjects who had an increase in hemoglobin ≥3.0 g/dL (91.4% versus 64.6%) at anytime during the study compared with the oral iron group. A greater proportion of FCM subjects compared with oral iron subjects had an increase in hemoglobin ≥3.0 g/dL on or before each visit; differences between the treatments groups were statistically significant at Days 14, 28, and 42.

Subgroup Analyses

The proportion of subjects who achieved hemoglobin >12.0 g/dL anytime during the study was examined for homogeneity of treatment response among subgroups in the Modified Intent-to-Treat, Evaluable, and Intent-to-Treat Populations.

In the Modified Intent-to-Treat Population (**Table 19**), statistically significantly greater proportions (Fisher's exact test) of subjects in the FCM group achieved a hemoglobin >12.0 g/dL compared with the oral iron group in each of the subgroups, except for subjects with a baseline hemoglobin ≥10.1 g/dL, subjects with a baseline ferritin >25 ng/dL, and subjects <19 years of age; however, the numbers of subjects in each of these subgroups was small. The confidence intervals (normal approximation method) for the differences in the proportions of subjects who achieved a hemoglobin ≥12.0 g/dL between the treatment groups demonstrated the superiority of FCM relative to oral iron in each of the subgroups, except for subjects with a baseline ferritin >25 ng/mL. No important differences were noted in the by-center analyses. In general, similar results were observed in the Evaluable and Intent-to-Treat Populations.

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Table 19. Summary of the Proportion of Subjects Who Achieved a Hemoglobin >12.0 g/dL Anytime During the Study by Subgroups (Study VIT-11: Modified Intent-to-Treat Population)

Strata	FCM n/N (%)	Oral Iron n/N (%)	Difference (95% CI)	Fisher's exact p-value
Baseline Hemoglobin				
≤8 g/dL	15/19 (78.9)	10/23 (43.5)	35.5 (27.19, 43.75)	0.0286
8.1-9.0 g/dL	38/42 (90.5)	29/ 49 (59.2)	31.3 (19.24, 43.34)	0.0008
9.1-10.0 g/dL	68/72 (94.4)	51/66 (77.3)	17.2 (4.02, 30.33)	0.0054
>10.1 g/dL	6/ 6 (100.0)	8/9 (88.9)	11.1 (4.75, 17.48)	>0.9999
Method of Delivery				
Caesarian	49/57 (86.0)	38/60 (63.3)	22.6 (9.80, 35.47)	0.0060
Vaginal	79/83 (95.2)	60/87 (69.0)	26.2 (13.41, 39.02)	<0.0001
Baseline Ferritin				
≤25 ng/mL	85/90 (94.4)	52/90 (57.8)	36.7 (23.81, 49.53	<0.0001
>25 ng/mL	42/49 (85.7)	46/57 (80.7)	5.0 (-7.85, 17.87)	0.6068
Age				
<19 years	13/ 14 (92.9)	4/ 7 (57.1)	35.7 (28.75, 42.68)	0.0877
≥19 years	114/125 (91.2)	94/140 (67.1)	24.1 (17.09, 31.02)	<0.0001
Race				
Caucasian	97/101 (96.0)	70/96 (72.9)	23.1 (11.60, 34.65)	<0.0001
Non-Caucasian	30/38 (78.9)	28/51 (54.9)	24.0 (12.52, 35.57)	0.0246

n = number of subjects who achieved endpoint, N = number of subjects in strata, % = 100 x (n / N), CI = confidence interval

2.5.2 Luitpold-Sponsored Study VIT-01: Comparison of the Safety and Efficacy of a Unique Intravenous Iron Preparation (FCM) Versus Oral Iron in Subjects who Display Postpartum Anemia

Study Objectives and Endpoints

Study VIT-01 was an open-label, Phase 3, randomized, active-controlled trial. The primary objective of this study was to evaluate the non-inferiority of intravenous FCM in comparison with oral iron in improving hemoglobin in postpartum anemia. The secondary objective of this study was to evaluate the safety and tolerability of intravenous FCM in comparison with oral iron in postpartum anemia.

The primary endpoint for efficacy was the proportion of subjects who achieved an increase in hemoglobin of ≥2 g/dL anytime between baseline and end of study or time of intervention.

The number and proportion of subjects who achieved an increase in hemoglobin of ≥2 g/dL on or before Day 7, Day 14, Day 28, and Day 42 were tabulated for each treatment group. Two summaries were provided. One was based on the observed cases method, the other was based on last observation carried forward method in which subjects who discontinued from the study prior to Day 42 were evaluated based on their last non-missing post baseline value.

Major secondary endpoints included:

- Proportion of subjects attaining an hemoglobin >12.0 g/dL at any time
- Proportion of subjects with an increase in hemoglobin ≥3 g/dL anytime between baseline and end of study or time of intervention
- Time to achieving an increase in hemoglobin of ≥2 g/dL

The Modified Intent-to-Treat Population was the primary population for evaluating all efficacy endpoints. The Evaluable Population was included as a supportive analysis.

Main Inclusion Criteria and Study Design

Postpartum subjects within 10 days after delivery with hemoglobin ≤10 g/dL at baseline based on the average of 2 hemoglobin values drawn ≥18 hours postpartum, met all inclusion/exclusion criteria, and had given informed consent were randomized. Subjects were screened for study entrance eligibility up to 5 weeks prior to expected delivery date. Within 10 days post-delivery, subjects meeting the criteria were randomized via an interactive voice response system (IVRS) into the treatment phase and received their first dose of study drug.

At randomization, subjects were stratified by hemoglobin levels (9.1-10.0 g/dL, 8.1-9.0 g/dL, ≤8.0 g/dL) and requirement for C-section and screening iron indices (serum transferrin saturation [TSAT] >20% and ferritin >50 ng/mL, TSAT ≤20% or ferritin ≤50 ng/mL). Subjects were randomly assigned to either FCM (up to a maximum cumulative iron dose of 2,500 mg administered intravenously based on iron deficit calculations; the calculated dose was given in divided doses of up to 1,000 mg weekly) or oral iron (325 mg of ferrous sulfate 3 times daily [TID] x 6 weeks). The administration of the initial dose of study drug could have occurred either during their inpatient stay or after discharge. Assessments for efficacy (complete blood count [CBC] and iron indices) and safety (adverse events and laboratory results) were performed on post-randomization Days 7, 14, 28, and 42.

Disposition

Three hundred sixty-one (361) subjects were randomized at 43 centers to receive FCM (182 subjects) or oral iron (179 subjects; **Table 20**). Of these 361 subjects, 8 randomized to FCM and 1 randomized to oral iron were discontinued from the study prior to dosing. Of the 8 subjects who were randomized to FCM, 3 were discontinued due to subject request, 2 were lost to follow-up, 2 due to "other" reasons, and 1 due to physician decision. The 1 subject that was randomized to oral iron was lost to follow-up. Therefore, a total of 174 subjects were treated in the FCM group and 178 were treated in the oral iron group.

One hundred sixty-five (165; 94.8%) of the 174 subjects in the FCM group and 162 (91.0%) of the 178 subjects in the oral iron group completed the study. Of the 9 subjects in the FCM group who did not complete the study, 4 discontinued due to subject request, 2 discontinued due to adverse events, 1 was lost to follow-up, 1 had an intervention and received non-study iron, and 1 discontinued due to "other" reasons.

Of the 16 subjects in the oral iron group who did not complete the study, 7 were lost to follow-up, 4 discontinued due to adverse events, 3 did not meet the selection/study compliance criteria, and 2 discontinued due to subject request.

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Table 20. Subject Disposition and Study Termination During the Treatment Phase (Study VIT-01)

	FCM	Oral Iron	Total
All Randomized Subjects	182	179	361
Treated Subjects	174 (100%)	178 (100%)	352 (100%)
Subjects Discontinued From Study	9 (5.2%)	16 (9.0%)	25 (7.1%)
Subject had intervention			
Received non-study iron	1 (0.6%)	0	
Did not complete study per protocol			
Adverse Event	2 (1.1%)	4 (2.2%)	
Selection Criteria/Study Compliance	0	3 (1.7%)	
Lost to Follow-Up	1 (0.6%)	7 (3.9%)	
Subject Request	4 (2.3%)	2 (1.1%)	
Other	1 (0.6%)	0	
Subjects Who Completed Study	165 (94.8%)	162 (91.0%)	327 (92.9%)

Demographic and Baseline Characteristics

No statistically significant differences were observed between the treatment groups among all treated subjects for age or race (**Table 21**).

Mean hemoglobin, TSAT, and ferritin values at baseline were similar between the FCM (9.00 g/dL, 10.54%, and 25.99 ng/mL, respectively) and oral iron (9.02 g/dL, 9.74%, 23.70 ng/mL, respectively) treatment groups. The proportion of subjects with a baseline hemoglobin ≤8.0 g/dL at randomization was 19.0% in the FCM group and 17.4% in the oral iron group.

The majority of the subjects in both treatment groups had received previous iron therapy (FCM: 82.8%; oral iron: 86.0%). Ten subjects (6 FCM and 4 oral iron) had a prior history of iron intolerance.

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Table 21. Demographic and Baseline Characteristics (Study VIT-01: All Treated Subjects)

	FCM (N=174)	Oral Iron (N=178)	p-value
Demographic Characteristic			
Age (years)			
Mean (SD)	26.93 (6.36)	26.03 (5.95)	0.168
Median	26.63	25.81	
Minimum – Maximum	14.95 – 49.15	15.27 – 39.99	
<19	15 (8.6%)	16 (9.0%)	1.000
≥19	159 (91.4%)	162 (91.0%)	
Race			
Caucasian	89 (51.1%)	78 (43.8%)	0.200
Hispanic	46 (26.4%)	57 (32.0%)	
African American	34 (19.5%)	39 (21.9%)	
Asian	2 (1.1%)	1 (0.6%)	
Other	3 (1.7%)	3 (1.7%)	
Baseline Characteristics			
Baseline Hemoglobin (g/dL)			0.807
Mean (SD)	9.00 (0.91)	9.02 (0.98)	
Median	9.23	9.20	
Minimum – Maximum	6.15 – 11.10	5.65 – 11.50	
Baseline TSAT (%)			0.280
Mean (SD)	10.54 (8.85)	9.74 (4.29)	
Median	9.00	9.00	
Minimum – Maximum	2.00 – 77.00	4.00 – 30.00	
Baseline Ferritin (ng/mL)			0.482
Mean (SD)	25.99 (36.01)	23.70 (23.76)	
Median	16.70	16.65	
Minimum – Maximum	3.10 – 375.80	2.60 – 175.70	
Prior Iron Intolerance			0.539
Yes	6 (3.4%)	4 (2.2%)	
Previous Iron Therapy			0.464
Yes	144 (82.8%)	153 (86.0%)	

SD=Standard Deviation

Extent of Exposure and Compliance

Among all treated subjects, the mean milligram (± SD) exposure during the study, calculated as the total dose of study drug (elemental iron) administered, was 1403.1 (± 390.69) mg in the FCM group and 6764.0 (± 2575.82) mg in the oral iron group (**Table 22**).

Table 22. Summary of Extent of Exposure (Study VIT-01: All Treated Subjects)

Total Dose of Iron (mg) Received	FCM	Oral Iron
All Treated Subjects	(N=174)	(N=178)
Mean (SD)	1403.1 (390.69)	6764.0 (2575.82)
95% Confidence Interval of Mean	1344.64, 1461.56	6383.01, 7145.02
Median	1400	7995
Minimum – Maximum	100 - 2500	65 - 9360

SD=Standard Deviation

In the Modified Intent-to-Treat Population, mean study drug usage was higher in the FCM treatment group compared with the oral iron treatment group. The proportion of subjects who used at least 67% of study drug was higher in the FCM treatment group compared with the oral iron group (**Table 23**).

Table 23. Summary of Study Drug Usage During the Treatment Phase (Study VIT-01 Modified Intent-to-Treat Population)

% Compliance	FCM	Oral Iron
	(N=168)	(N=169)
Total Iron Received/Total Iron Expected Based on Actual Days on Study		
Mean (SD)	98.0 (14.61)	83.9 (25.00)
95% Confidence Interval of Mean	95.75, 100.20	80.09, 87.68
Median	100	95
Minimum – Maximum	8 – 175	1 – 112
Subjects ≥67% Compliant	162 (96.43%)	141 (83.43%)

Datasets Analyzed

All subjects (N=337) who had documented postpartum anemia at baseline (characterized by the average of the 2 baseline central laboratory hemoglobin measurements being <11.0 g/dL), received at least 1 dose of study medication, and had at least 1 post-baseline hemoglobin assessment were included in the Modified Intent-to-Treat Population (**Table 24**). All subjects in the Modified Intent-to-Treat Population who received at least 67% of required study drug, were followed until the Day 42 evaluation, and had no major protocol violations (N=312) were included in the Evaluable Population.

Table 24. Datasets Analyzed (Study VIT-01)

Population	FCM (N=174)	Oral Iron (N=178)
Modified Intent-to-Treat Population	168 (96.6%)	169 (94.9%)
Evaluable Population	162 (93.1%)	150 (84.3%)

Analyses of an Intent-to-Treat Population were not specified in the statistical analysis plan for Study VIT-01. However, a post hoc analysis of all randomized subjects, regardless of whether or not they had received a dose of study medication, was performed and results were previously presented in **Table 10**.

Efficacy

The primary efficacy endpoint was the proportion of subjects who achieved an increase in hemoglobin ≥2.0 g/dL at anytime between baseline and the end of study or time of intervention. The primary efficacy analysis was the non-inferiority of the proportion of subjects who achieved an increase in hemoglobin of ≥2 g/dL for FCM relative to oral iron based on a 1-sided 97.5% confidence interval on the treatment difference with a non-inferiority margin of 15%. The confidence interval was constructed from the unstratified comparison of the rate using the normal approximation to the binomial distribution. If non-inferiority was established as described above, superiority of FCM compared to oral iron was assessed and was declared if the lower bound of the confidence interval was greater than zero. The Modified Intent-to-Treat Population was the primary population for evaluating all efficacy endpoints. The Evaluable Population was included as a supportive analysis.

Although the total dose of iron received in the oral iron group was more than 4 times that received in the FCM group, the proportions of subjects who achieved a ≥2 g/dL increase in hemoglobin, was similar between the FCM (96.4%) and oral iron (94.1%) treatment groups and non-inferiority of FCM relative to oral iron was demonstrated (**Table 25**).

Table 25. Summary of the Proportion of Subjects Who Achieved a ≥2.0 g/dL Increase From Baseline in Hemoglobin at Anytime During the Study (Study VIT-01: Modified Intent-to-Treat and Evaluable Populations)

≥2 g/dL Increase From Baseline in Hemoglobin Anytime During Study	Number (%) Subjects		Fisher's Exact p-value	95% CI
	FCM n/N (%)	Oral Iron n/N (%)		
Modified Intent-to-Treat Population	162/168 (96.4%)	159/169 (94.1%)	0.4433	-2.19, 6.88
Evaluable Population	158/162 (97.5%)	142/150 (94.7%)	0.2432	-1.26, 6.99

n = number of subjects who achieved an increase in hemoglobin of ≥2 g/dL, N = number of subjects in group, % = n divided by N
CI = confidence interval based on normal approximation to the binomial

A greater proportion of FCM subjects compared with oral iron subjects achieved an increase in hemoglobin of ≥2 g/dL on or before each visit; differences between the treatments groups were statistically significant at Days 7, 14, and 28 for subjects with data at these timepoints. Subjects in the FCM group achieved an increase in hemoglobin of ≥2 g/dL earlier compared with subjects in the oral iron group, with statistically significant differences observed as early as Day 7 (58.3% vs. 38.5%; **Table 26**). Additionally, the median time to achieve an increase in hemoglobin of ≥2 g/dL was statistically significantly shorter for FCM subjects (7.0 days) compared with oral iron (14.0 days) subjects.

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Table 26. Summary of the Proportion of Subjects Who Achieved a ≥2.0 g/dL Increase From Baseline in Hemoglobin on or Before Each Visit During the Study (Study VIT-01: Modified Intent-to-Treat Populations)

Day	FCM n/N (%)		Oral Iron n/N (%)		Fisher's Exact p-value	
	LOCF	OC	LOCF	OC	LOCF	OC
VIT-01: Increase in Hb ≥2 g/dL on or before reference day						
7	98/168 (58.3%)	98/168 (58.3%)	65/169 (38.5%)	65/164 (39.6%)	0.0003	0.0007
14	147/168 (87.5%)	144/167 (86.2%)	122/169 (72.2%)	111/162 (68.5%)	0.0006	0.0001
28	160/168 (95.2%)	153/163 (93.9%)	151/169 (89.3%)	139/163 (85.3%)	0.0644	0.0174
42	162/168 (96.4%)	151/163 (92.6%)	159/169 (94.1%)	143/161 (88.8%)	0.4433	0.2556

n = number of subjects who achieved endpoint, N = number of subjects in group, % = 100 x (n divided by N), LOCF = last observation carried forward, OC = observed cases

The FCM group had a statistically significantly greater proportion of subjects who achieved hemoglobin concentrations >12.0 g/dL (90.5% vs. 68.6%) and who had an increase in hemoglobin ≥3.0 g/dL (86.3% vs. 60.4%) at anytime during the study compared with the oral iron group. FCM subjects with baseline hemoglobin concentrations ≤10.0 g/dL achieved better responses than oral iron subjects, while responses among subjects with baseline hemoglobin concentrations ≥10.1 g/dL were similar between the treatment groups.

Results were generally consistent across subgroups defined by baseline hemoglobin, method of delivery, baseline TSAT and ferritin, age, race and center for the primary efficacy parameter (**Table 27**).

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Table 27. Summary of the Proportion of Subjects Who Achieved a Hemoglobin >2.0 g/dL Anytime During the Study by Subgroups (Study VIT-01: Modified Intent-to-Treat Population)

Strata	FCM n/N (%)	Oral Iron n/N (%)	Difference (95% CI)
Baseline Hemoglobin			
≤8 g/dL	28/28 (100.0)	24/25 (96.0)	4.0 (0.95, 7.05)
8.1-9.0 g/dL	45/45 (100.0)	41/45 (91.1)	8.9 (4.47, 13.31)
9.1-10.0 g/dL	78/82 (95.1)	77/80 (96.3)	-1.2 (-5.57, 3.31)
>10.1 g/dL	11/13 (84.6)	17/19 (89.5)	-4.9 (-12.18, 2.46)
Method of Delivery			
Caesarian	80/82 (97.6)	74/77 (96.1)	1.5 (-2.38, 5.29)
Vaginal	82/86 (95.3)	85/92 (92.4)	2.9 (-2.29, 8.20)
Baseline TSAT and Ferritin			
TSAT >20% and Ferritin >50 ng/mL	2/ 2 (100.0)	0	NC
TSAT≤20% or Ferritin ≤50 ng/mL	160/166 (96.4)	159/169 (94.1)	2.3 (-2.36, 6.96)
Age			
<19 years	15/15 (100.0)	15/16 (93.8)	6.2 (2.49, 10.01)
≥19 years	147/153 (96.1)	144/153 (94.1)	2.0 (-2.76, 6.68)
Race			
Caucasian	85/88 (96.6)	73/77 (94.8)	1.8 (-2.65, 6.23)
Non-Caucasian	77/80 (96.3)	86/92 (93.5)	2.8 (-2.05, 7.60)

n = number of subjects who achieved endpoint, N = number of subjects in strata, % = 100 x (n / N), CI = confidence interval, NC = not calculated

2.5.3 European-Sponsored Study VIT-09: A Multicenter, Controlled, Phase 3 Study to Investigate the Safety and Efficacy of Intravenous Infusions of FCM in Women Suffering From Postpartum Anemia

Study Objectives and Primary Endpoint

Study VIT-09 was a multicenter, open-label, randomized, controlled, parallel-group Phase 3 study. The primary objective of the study was to evaluate the non-inferiority efficacy of intravenous FCM in comparison with oral iron in reducing IDA in women with post-partum anemia. The secondary objectives were to investigate the safety and tolerability of FCM in comparison with oral iron. The primary endpoint was assessed through the change from baseline levels of hemoglobin to Week 12.

Main Inclusion Criteria and Study Design

The study enrolled adult women with postpartum anemia within 6 days after delivery defined as a hemoglobin ≤10.5 g/dL based on the average of 2 assessments drawn on different days within 48 to 96 hours post-partum. To be eligible, both values had to be ≤10.5 g/dL or, if 1 of the 2 hemoglobin values was >10.5 g/dL, the average of both hemoglobin values had to be ≤10.5 g/dL and the difference between the 2 samples could not be >1 g/dL.

The study consisted of 3 screening visits. All screening assessments were done at Screening 1 within 14 days before the estimated date of delivery (no more than 5 weeks before delivery).

Screenings 2 and 3 consisted of hemoglobin assessments only, and were done 48-96 hours postpartum. During the screening period, subjects were enrolled into the study on the basis of the inclusion and exclusion criteria. Baseline assessments were done on Day 1, Week 0 prior to the first dose of study drug. Subjects were randomized in a 2:1 (FCM:oral iron) ratio to receive 1 of 2 treatments: intravenous FCM on Day 1 with subsequent doses at 1-week intervals until the subject's calculated cumulative dose was reached (up to a maximum of 3 infusions), or oral iron capsules 100 mg twice daily (BID) for 12 weeks. All subjects returned for assessments of efficacy and safety at Weeks 1 (only the FCM group who received drug), 2, 4 and 12.

Disposition

Twenty centers in 3 countries randomized 349 subjects in the study (**Table 28**). Of these 349 subjects, 344 received at least 1 dose of study drug (FCM: 227; oral iron: 117).

Table 28. Subject Disposition and Study Termination (Study VIT-09)

	FCM	Oral Iron	Overall
All Randomized Subjects			349
All Treated Subjects	227	117	344
Subjects Discontinued From Study	29 (12.8%)	15 (12.8%)	44 (12.8%)
Adverse Event	3 (1.3%)	1 (0.9%)	4 (1.2%)
Patient withdrew consent	13 (5.7%)	7 (6.0%)	20 (5.8%)
Lost to follow up	7 (3.1%)	3 (2.6%)	10 (2.9%)
Non-compliance with study procedures	6 (2.6%)	4 (3.4%)	10 (2.9%)

Demographic and Baseline Characteristics

Overall, most subjects were Caucasian (99.3%) and from Romania (54.5%). The mean age was 27.6 years. The subjects' demographic data were similar between the treatment groups.

Extent of Exposure

The mean total dose for FCM was 1346.7 mg (range 600 to 2200 mg), and the mean duration of treatment was 8.2 days (range 1 to 17 days). The mean total dose for oral iron was 15520 mg (range: 1200 to 21000 mg).

Datasets Analyzed

Out of 349 randomized subjects, 344 were included in the Intent-to-Treat Population, as they had received at least 1 dose of study drug and had efficacy data available, and 268 patients were included in the Evaluable Population. A total of 76 subjects were excluded from the Evaluable Population; 32 due to major protocol violations and 44 due to premature discontinuation.

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Efficacy

In the Evaluable Population, the mean hemoglobin concentration increased from 9.67 g/dL (FCM) and 9.60 g/dL (oral iron) at baseline to 13.04 g/dL (FCM) and 12.89 g/dL (oral iron) at Week 12, which resulted in a mean increase of hemoglobin of 3.37 g/dL in the FCM group and a mean increase of 3.29 g/dL in the oral iron group. There was no significant difference between the 2 groups in change from baseline to Week 12.

The lower bound of the 95% confidence intervals for the difference "FCM – oral iron" was –0.69 for the Evaluable Population and –1.47 for the Intent-to-Treat Population and thus above the pre-specified non-inferiority margin of -5 g/L; thus non-inferiority of FCM versus oral iron was demonstrated. However, superiority was not concluded, because the lower limits of the confidence intervals were below zero.

2.5.4 Luitpold-Sponsored Study VIT-02/VIT-03: Comparison of the Safety and Efficacy of a Unique Intravenous Iron Preparation (FCM) Versus Oral Iron in the Treatment of Iron Deficiency Anemia Secondary to Heavy Uterine Bleeding

Study Objectives and Endpoints

Study VIT-02/VIT-03 was the result of combining 2 open-label, Phase 3, randomized, active-controlled studies with 2 parallel treatment groups. Due to slow enrollment, it was decided to combine the data from the 2 studies (VIT-02 and VIT-03). The statistical analysis plan for the combined analysis was finalized prior to completion of enrollment. Additionally, the statistical analysis plan specified that the primary endpoint and all ranked secondary endpoints would be presented for the combined analysis and for each study separately.

The primary objective of this study was to demonstrate that the efficacy of intravenous FCM is superior to oral iron in improving hemoglobin in females with IDA secondary to HUB. The secondary objective was to evaluate the safety and tolerability of intravenous FCM in comparison with oral iron in females with IDA secondary to HUB.

The primary endpoint for efficacy was the proportion of subjects achieving an increase from baseline in hemoglobin of ≥2.0 g/dL anytime between baseline and end of study or time of intervention.

Major secondary endpoints included:

- Proportion of subjects attaining an hemoglobin >12.0 g/dL at any time between baseline and end of study or time of intervention
- Proportion of subjects with an increase in hemoglobin ≥3 g/dL anytime between baseline and end of study or time of intervention
- Time to achieving an increase from baseline in hemoglobin of ≥2.0 g/dL

The Modified Intent-to-Treat Population was the primary population for evaluating all efficacy endpoints. The Evaluable Population was included as a supportive analysis.

Main Inclusion Criteria and Study Design

Females with a history of HUB within the past 6 months, a hemoglobin ≤11 g/dL at Baseline based on the average of 2 hemoglobin values drawn on different days within a 7-day period and whose difference was ≤0.7 g/dL, a baseline TSAT ≤25%, a baseline ferritin ≤100 ng/mL, who met all inclusion/exclusion criteria, and had given informed consent were randomized. The duration of the study for each subject was a maximum of 9 weeks. Subjects were screened for study entrance eligibility 2 to 3 weeks prior to the first day of study drug (Day 0). The screening process included a careful history of past oral iron use and response. Subjects meeting the criteria for randomization were randomized into the 42-day Treatment Phase and received their first dose of study drug on Day 0.

At randomization, subjects were stratified by hemoglobin levels (9.6-11.0 g/dL, 8.1-9.5 g/dL, ≤8.0 g/dL), degree of uterine bleeding (mild/moderate, severe or very severe) during the past 28 days and by past response to oral iron. Subjects were randomly assigned to either FCM (up to a maximum cumulative iron dose of 2500 mg administered intravenously based on iron deficit calculations given in divided doses of up to 1,000 mg weekly) or oral iron (325 mg of ferrous sulfate TID x 42 days) and immediately began the 42 day Treatment Phase where they were followed for safety and efficacy. Assessments for efficacy included hematologic parameters, iron indices, and Quality of Life (QOL) questionnaires. Uterine blood loss was assessed indirectly throughout the study with the use of the Pictorial Blood Loss Assessment Chart (PBAC) and subject and physician rating of bleeding symptoms.

Disposition

Four hundred seventy-seven (477) subjects were randomized at 84 centers to receive either FCM (246 subjects) or oral iron (231 subjects; **Table 29**). Two hundred fifty-seven (257) subjects were randomized at 43 centers into Study VIT-02 to receive either FCM (131 subjects) or oral iron (126 subjects) and 220 subjects were randomized at 41 centers into Study VIT-03 to receive either FCM (115 subjects) or oral iron (105 subjects). Of these 477 subjects, 16 randomized to FCM and 5 randomized to oral iron were discontinued from the study prior to dosing. Of the 16 subjects who were randomized to FCM, 9 were discontinued due to subject request, 4 due to "other" reasons, 2 were lost to follow-up, and 1 required intervention. Of the 5 subjects who were randomized to oral iron, 3 were discontinued due to "other" reasons and 2 were discontinued due to subject request. Therefore, a total of 230 subjects were treated in the FCM group and 226 were treated in the oral iron group.

Two hundred eleven (211; 91.7%) of the 230 subjects in the FCM group and 212 (93.8%) of the 226 subjects in the oral iron group completed the study. Of the 19 subjects in the FCM group who did not complete the study, 7 discontinued due to "other" reasons, 6 discontinued due to subject request, 2 discontinued due to adverse events, 2 were lost to follow-up, 1 discontinued due to pregnancy, and 1 had an intervention and received non-study iron.

Of the 14 subjects in the oral iron group who did not complete the study, 3 discontinued due to adverse events, 3 discontinued due to subject request, 3 discontinued due to "other" reasons, 2 were lost to follow-up, and 3 had an intervention and received medication/procedure to decrease uterine bleeding.

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Table 29. Subject Disposition and Study Termination During the Treatment Phase (Study VIT-02/VIT-03)

	FCM	Oral Iron	Total
All Randomized Subjects	246	231	477[a]
Treated Subjects	230	226	456
Subjects Discontinued From Study	19 (8.3%)	14 (6.2%)	33 (7.2%)
Subjects required intervention	1 (0.4%)	3 (1.3%)	4 (0.9%)
Received non-study iron	1 (0.4%)	0	1 (0.2%)
Medication/procedure to decrease uterine bleeding	0	3 (1.3%)	3 (0.7%)
Subjects did not complete the study	18 (7.8%)	11 (4.9%)	29 (6.4%)
Adverse Event	2 (0.9%)	3 (1.3%)	5 (1.1%)
Pregnancy	1 (0.4%)	0	1 (0.2%)
Lost to Follow-Up	2 (0.9%)	2 (0.9%)	4 (0.9%)
Subject Request	6 (2.6%)	3 (1.3%)	9 (2.0%)
Other	7 (3.0%)	3 (1.3%)	10 (2.2%)
Subjects Who Completed Study	211 (91.7%)	212 (93.8%)	423 (92.8%)

a Eight subjects (7 subjects due to natural disaster) were excluded from the analyses due to loss of source documents.

Demographic and Baseline Characteristics

A statistically significant difference was observed between the treatment groups among all treated subjects for pattern of menstrual cycle at screening; a greater proportion of subjects in the oral iron group had regular menstrual cycles at screening (74.3%) compared with subjects in the FCM group (65.1%). No other statistically significant differences were observed between the treatment groups for any of the demographic characteristics (**Table 30**).

Mean hemoglobin, TSAT, and ferritin values at baseline were similar between the FCM (9.41 g/dL, 5.90%, and 6.85 ng/mL, respectively) and oral iron (9.44 g/dL, 5.63%, 6.80 ng/mL, respectively) treatment groups. The proportion of subjects with baseline hemoglobin ≤8.0 g/dL at randomization was 13.9% in the FCM group and 14.2% in the oral iron group. The mean days of bleeding per month and mean days of heavy bleeding per month were 8.3 and 4.6 in the FCM group and 8.5 and 4.4 in the oral iron group, respectively. The majority of the subjects in both treatment groups had received previous iron therapy (FCM: 69.1%; oral iron: 69.9%). Fifty-four subjects (23 FCM and 31 oral iron) had a prior history of iron intolerance to 1 or more iron products.

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Table 30. Demographic and Baseline Characteristics (Study VIT-02/VIT-03: All Treated Subjects)

	FCM (N=230)	Oral Iron (N=226)	p-value
Demographic Characteristic			
Age (years)			0.264
Mean (SD)	38.7 (7.49)	39.5 (7.63)	
Median	40	41	
Minimum – Maximum	18 – 54	19 – 53	
Race			0.916
African American	115 (50.0%)	105 (46.5%)	
Caucasian	63 (27.4%)	60 (26.5%)	
Hispanic	46 (20.0%)	57 (25.2%)	
Other	4 (1.7%)	3 (1.3%)	
Asian	2 (0.9%)	1 (0.4%)	
Menstrual Cycle*			0.031
Regular	149 (65.1%)	168 (74.3%)	
Irregular	78 (34.1%)	53 (23.5%)	
Continuous	2 (0.9%)	5 (2.2%)	
Missing	1	0	
Degree of Bleeding			0.972
Mild/Moderate	98 (42.6%)	94 (41.6%)	
Severe	107 (46.5%)	108 (47.8%)	
Very Severe	25 (10.9%)	24 (10.6%)	
Baseline Characteristics			
Baseline Hemoglobin (g/dL)			0.832
Mean (SD)	9.41 (1.234)	9.44 (1.229)	
Median	9.6	9.7	
Minimum – Maximum	4.9 – 11.1	5.5 – 11.1	
Baseline TSAT (%)			0.471
Mean (SD)	5.90 (4.095)	5.63 (3.653)	
Median	4.7	4.8	
Minimum – Maximum	1.6 – 24.5	1.3 – 25.0	
<20	227 (98.7%)	222 (98.2%)	
Baseline Ferritin (ng/mL)			0.948
Mean (SD)	6.85 (9.217)	6.80 (8.819)	
Median	4.1	4.1	
Minimum – Maximum	1.5 – 81.6	1.3 – 73.6	
<100	230 (100.0%)	226 (100.0%)	
Prior Iron Intolerance			0.247
Yes	23 (10.0%)	31 (13.7%)	
Previous Iron Therapy			0.919
Yes	159 (69.1%)	158 (69.9%)	

SD=Standard Deviation
* Statistically significant difference between treatment groups at the $p<0.05$ level.

Extent of Exposure and Compliance

Among all treated subjects, the mean milligram (± SD) exposure during the study, calculated as the total dose of study drug (elemental iron) administered, was 1567.7 (± 422.28) mg in the FCM group and 7302.1 (± 1937.15) mg in the oral iron group (**Table 31**).

Table 31. Summary of Extent of Exposure (Study VIT-02/VIT-03: All Treated Subjects)

Total Dose of Iron (mg) Received	FCM	Oral Iron
All Treated Subjects	(N=230)	(N=226)
Mean (SD)	1567.7 (422.28)	7302.1 (1937.15)
Median	1500	7995
Minimum – Maximum	0 – 2500	65 – 9750

SD=Standard Deviation

In the Modified Intent-to-Treat Population, mean study drug usage was higher in the FCM treatment group compared with the oral iron treatment group. The proportion of subjects who used at least 67% of study drug was higher in the FCM treatment group compared with the oral iron group **Table 32**.

Table 32. Summary of Study Drug Usage During the Treatment Phase (Study VIT-02/VIT-03: Modified Intent-to-Treat Population)

% Compliance	FCM	Oral Iron
	(N=228)	(N=225)
Total Iron Received/Total Iron Expected Based on Actual Days on Study		
Mean (SD)	99.9 (9.65)	90.3 (19.16)
95% Confidence Interval of Mean	98.67, 101.18	87.83, 92.84
Median	100	98
Minimum – Maximum	26 – 183	1 – 118
Subjects ≥67% Compliant	225 (98.7%)	202 (89.8%)

Datasets Analyzed

All subjects (N=453) who received at least 1 dose of study medication, had average baseline central laboratory hemoglobin ≤11.1 g/dL, baseline TSAT ≤25%, and baseline ferritin ≤100 ng/mL, had HUB at baseline, and had at least 1 post-baseline hemoglobin assessment were included in the Modified Intent-to-Treat Population (**Table 33**). All subjects in the Modified Intent-to-Treat Population who received at least 67% of required study drug, were followed until the Day 42 evaluation, and had no major protocol violations (N=420) were included in the Evaluable Population.

Table 33. Datasets Analyzed (Study VIT-02/VIT-03)

Population	FCM (N=230)	Oral Iron (N=226)
Modified Intent-to-Treat Population	228 (99.1%)	225 (99.6%)
Evaluable Population	213 (92.6%)	207 (91.6%)

Analyses of an Intent-to-Treat Population were not specified in the statistical analysis plan for Study VIT-02/VIT-03. However, a post hoc analysis of all randomized subjects, regardless of whether or not they had received a dose of study medication, was performed and results were previously presented in (**Table 10**).

Efficacy

The primary efficacy endpoint was the proportion of subjects who achieved an increase in hemoglobin ≥2.0 g/dL at anytime between baseline and the end of study or time of intervention. The primary efficacy analysis was the superiority of the proportion of subjects who achieved an increase from baseline in hemoglobin of ≥2.0 g/dL anytime between baseline and end of study or time of intervention for FCM relative to oral iron based on a 2-sided Fisher's exact test. The Modified Intent-to-Treat Population was the primary population for evaluating all efficacy endpoints. The Evaluable Population was included as a supportive analysis.

Among subjects in the Modified Intent-to-Treat Population, there was a statistically significantly greater proportion of FCM subjects (187/228; 82.0%) who achieved an increase in hemoglobin of ≥2.0 g/dL during the study compared with oral iron subjects (139/225; 61.8%; **Table 34**), although the total dose of iron received in the oral iron group was more than 4 times that received in the FCM group. Similar results were observed in the Evaluable Population.

Table 34. Summary of the Proportion of Subjects Who Achieved a ≥2.0 g/dL Increase From Baseline in Hemoglobin at Anytime During the Study (Study VIT-02/VIT-03: Modified Intent-to-Treat and Evaluable Populations)

≥2 g/dL Increase From Baseline in Hemoglobin Anytime During Study	Number (%) Subjects		Fisher's Exact p-value	95% CI
	FCM n/N (%)	Oral Iron n/N (%)		
Modified Intent-to-Treat 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

n = number of subjects who achieved an increase from baseline in hemoglobin of ≥2.0 g/dL anytime between baseline and end of study or time of intervention, N = number of subjects in group, % = 100 x (n divided by N)
CI = confidence interval for treatment difference based on normal approximation to the binomial

Statistically significant superiority of FCM to oral iron was also observed in the individual studies of VIT-02 and VIT-03, providing 2 prospectively planned studies that independently indicated the superiority of FCM to oral iron (**Table 35**). Among subjects in the Modified Intent-to-Treat Population in Study VIT-02, there was a statistically significantly (p<0.001) greater proportion of FCM subjects (99/120; 82.5%) who achieved an increase from baseline in hemoglobin of ≥2.0 g/dL anytime between baseline and end of study or time of intervention compared with oral iron subjects (80/126; 63.5%). Among subjects in the Modified Intent-to-Treat Population in Study VIT-03, there was a statistically significantly (p<0.001) greater proportion of FCM subjects (88/108; 81.5%) who achieved an increase from baseline in hemoglobin of ≥2.0 g/dL anytime between baseline and end of study or time of intervention compared with oral iron subjects (59/99; 59.6%).

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Table 35. Summary of the Proportion of Subjects Who Achieved a ≥2.0 g/dL Increase From Baseline in Hemoglobin at Anytime During the Study (Studies VIT-02 and VIT-03: Modified Intent-to-Treat Populations)

≥2 g/dL Increase From Baseline in Hemoglobin Anytime During Study	Number (%) Subjects		Fisher's Exact p-value	95% CI
	FCM n/N (%)	Oral Iron n/N (%)		
Study VIT-02	99/120 (82.5%)	80/126 (63.5%)	<0.001	8.2, 29.8
Study VIT-03	88/108 (81.5%)	59/99 (59.6%)	<0.001	9.8, 34.0

n = number of subjects who achieved an increase from baseline in hemoglobin of ≥2.0 g/dL anytime between baseline and end of study or time of intervention N = number of subjects in group, % = 100 x (n divided by N)
CI = confidence interval for treatment difference based on normal approximation to the binomial

A hemoglobin >12.0 g/dL at anytime during the study was achieved by a statistically significantly greater proportion of FCM subjects (166/228; 72.8%) compared with oral iron subjects (112/225; 49.8%). In addition, a statistically significant difference was observed between the FCM (121/228; 53.1%) and oral iron (80/225; 35.6%) groups in the proportion of subjects who had an increase in hemoglobin of ≥3.0 g/dL during the study.

Subjects in the FCM group achieved an increase from baseline in hemoglobin of ≥2.0 g/dL earlier compared with subjects in the oral iron group, with statistically significant differences observed as early as Day 7 (**Table 36**).

Table 36. Summary of the Proportion of Subjects Who Achieved a ≥2.0 g/dL Increase From Baseline in Hemoglobin on or Before Each Visit During the Study (Study VIT-02/VIT-03: Modified Intent-to-Treat Populations)

Day	FCM n/N (%)		Oral Iron n/N (%)		Fisher's Exact p-value	
	LOCF	OC	LOCF	OC	LOCF	OC
VIT-02/VIT-03: Increase in Hb ≥2 g/dL on or before reference day						
7	15/219 (6.8%)	15/219 (6.8%)	6/222 (2.7%)	6/222 (2.7%)	0.046	0.046
14	87/228 (38.2%)	85/219 (38.8%)	59/225 (26.2%)	56/218 (25.7%)	0.007	0.004
28	155/228 (68.0%)	147/215 (68.4%)	109/225 (48.4%)	102/215 (47.4%)	<0.001	<0.001
42	187/228 (82.0%)	163/212 (76.9%)	139//225 (61.8%)	120/209 (57.4%)	<0.001	<0.001

n = number of subjects who achieved endpoint, N = number of subjects in group, % = 100 x (n divided by N), LOCF = last observation carried forward, OC = observed cases

The superiority of FCM versus oral iron for efficacy was consistent across baseline hemoglobin level, degree of uterine bleeding at baseline, baseline levels of TSAT and ferritin, history of poor response to oral iron, total dose of iron, and race (**Table 37**).

Table 37. Summary of the Proportion of Subjects Who Achieved a Hemoglobin >2.0 g/dL Anytime During the Study by Subgroups (Study VIT-02/VIT-03: Modified Intent-to-Treat Population)

Strata	FCM n/N (%)	Oral Iron n/N (%)	Difference (95% CI)	Fisher's exact p-value
Baseline Hemoglobin				
≤8 g/dL	31/32 (96.9)	27/32 (84.4)	12.5 (-1.5, 26.5)	0.196
8.1-9.5 g/dL	79/81 (97.5)	53/75 (70.7)	26.9 (16.0, 37.7)	<0.001
9.6-11.1 g/dL	77/115 (67.0)	59/118 (50.0)	17.0 (4.5, 29.4)	0.011
Degree of Uterine Bleeding				
Mild/Moderate	76/98 (77.6)	53/94 (56.4)	21.2 (8.2, 34.2)	0.002
Severe	89/105 (84.8)	72/108 (66.7)	18.1 (6.9, 29.3)	0.002
Very Severe	22/25 (88.0)	14/23 (60.9)	27.1 (3.5, 50.8)	0.046
History of Poor Response to Oral Iron				
No	137/167 (82.0)	100/153 (65.4)	16.7 (7.2, 26.2)	<0.001
Yes	50/61 (82.0)	39/72 (54.2)	27.8 (12.8, 42.8)	<0.001
Total Dose of Iron				
≤1000 mg	9/ 13 (69.2)	0/ 7 (0.0)	69.2 (44.1, 94.3)	0.005
>1000 mg	178/215 (82.8)	139/218 (63.8)	19.0 (10.9, 27.2)	<0.001
Race				
Caucasian	53/63 (84.1)	43/60 (71.7)	12.5 (-2.1, 27.0)	0.127
Non-Caucasian	134/165 (81.2)	96/165 (58.2)	23.0 (13.4, 32.6)	<0.001

n = number of subjects who achieved endpoint, N = number of subjects in strata, % = 100 x (n / N), CI = confidence interval

2.5.5 Overall Efficacy Conclusions

The 3 postpartum studies consistently demonstrated clinically significant increases in hemoglobin from baseline following treatment with FCM. In Study VIT-11, the proportion of subjects in the Modified Intent-to-Treat Population who achieved the protocol-specified primary endpoint of a hemoglobin >12.0 g/dL anytime during the study was statistically significantly greater in the FCM group (91.4%) compared with the oral iron group (66.7%). This definition was specified in Study VIT-11 partly because a hemoglobin >12.0 g/dL corresponds to the lower limit of the hemoglobin laboratory reference range in this population. Additionally, this clinically relevant criterion is less sensitive to the inherent hemoglobin increases of postpartum subjects due to post-delivery diuresis.

The FCM group in the earlier VIT-01 study also had a statistically significantly greater proportion of subjects who achieved hemoglobin concentrations >12.0 g/dL (90.5% vs. 68.6%). The primary endpoint in Study VIT-01 was an increase in hemoglobin from baseline of ≥2 g/dL and the protocol-specified non-inferiority criterion was met for this endpoint. The observed non-inferiority of FCM to oral iron for the protocol-specified endpoint, in conjunction with the statistically significant treatment group differences for the endpoints of hemoglobin >12.0 g/dL and hemoglobin increase ≥3 g/dL, support the hypothesis that sensitive endpoints for postpartum anemia must be relatively robust in the presence of inherent hemoglobin increases after delivery. This was the rationale for choosing the primary endpoint in Study VIT-11, and results from Study VIT-11 confirmed the choice.

Study VIT-09 allowed randomized subjects to have baseline hemoglobin values that did not meet the inclusion criterion for hemoglobin (<10.5 g/dL). For example, the baseline hemoglobin for 1 subject was 14.5 g/dL. Inclusion of subjects was based on the average of 2 screening hemoglobin values, and the baseline hemoglobin was measured up to 3 days after the second screening value. Thus, 62 subjects in the evaluable population (41 FCM and 21 oral iron) had baseline hemoglobin values >10.5 g/dL. The inclusion of these subjects tends to minimize the increase from baseline and obscure treatment group differences.

The primary endpoint in Study VIT-02/VIT-03 was the proportion of subjects achieving an increase from baseline in hemoglobin of ≥2.0 g/dL. In contrast to the postpartum populations, subjects with HUB tend to have inherent hemoglobin decreases over time because of continuing blood loss. Thus, statistically significant superiority of FCM to oral iron was demonstrated for this criterion.

For the primary efficacy endpoint in each study, the superiority of FCM to oral iron was first demonstrated statististically at Day 7 (VIT-01 and VIT-02/VIT-03) or Day 14 (VIT-11). These results suggest that FCM may be especially useful in patients who require rapid correction of hemoglobin (e.g., pre-surgical).

Adherence to treatment was high in both the FCM and oral iron groups across the studies in women's health. Assuming that adherence to oral iron therapy in clinical practice will be lower than in these studies, the efficacy of oral iron will actually be less in clinical practice. In contrast, adherence to FCM and its efficacy should be similar between clinical trials and clinical practice. Therefore, the superiority of FCM to oral iron in clinical practice may be underestimated in these clinical trials.

The data from each of the randomized, controlled, parallel-group studies conducted in the women's health population demonstrate that FCM is effective in the treatment of IDA, including subjects with postpartum IDA and subjects with IDA secondary to HUB (**Table 38**). The clinical benefit is observed across demographic or baseline characteristics. Thus, FCM is an effective agent for the treatment of IDA in these populations.

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Table 38. Summary of Key Efficacy Endpoints from Randomized, Controlled, Parallel-Group Studies Sponsored by Luitpold in Postpartum and HUB Populations (Modified Intent-to-Treat Populations)

Efficacy Endpoint Achieved Anytime During Study	Number (%) Subjects		Fisher's Exact p-value	95% CI
	FCM n/N (%)	Oral Iron n/N (%)		
Modified Intent-to-Treat Population				
Hb >12 g/dL				
Study VIT-11*	127/139 (91.4%)	98/147 (66.7%)	<0.0001	15.20, 34.20
Study VIT-01	152/168 (90.5%)	116/169 (68.6%)	<0.0001	13.55, 30.12
Study VIT-02/VIT-03	166/228 (72.8%)	112/225 (49.8%)	<0.001	14.3, 31.7
Increase from BL in Hb ≥2 g/dL				
Study VIT-01*	162/168 (96.4%)	159/169 (94.1%)	non-inferiority trial	-2.19, 6.88
Study VIT-02/VIT-03*	187/228 (82.0%)	139/225 (61.8%)	<0.001	12.2, 28.3
Increase from BL in Hb ≥3 g/dL				
Study VIT-11	127/139 (91.4%)	95/147 (64.6%)	<0.0001	17.08, 36.41
Study VIT-01	145/168 (86.3%)	102/169 (60.4%)	<0.0001	16.93, 34.98
Study VIT-02/VIT-03	121/228 (53.1%)	80//225 (35.6%)	<0.001	8.5, 26.5

* Primary endpoint
n = number of subjects who achieved endpoint, N = number of subjects in group, % = n divided by N
CI = confidence interval based on normal approximation to the binomial

2.6 Safety

Safety summaries from the FCM clinical program presented in this section are primarily based on the incidences of adverse events, premature discontinuation of study drug due to adverse events, serious adverse events, and deaths. Additionally, presentations of possible predictors of adverse events (dose and maximum hemoglobin concentration) and adverse events of special interest including hypotension, allergic reactions, bioactive iron reactions, infections, cardiovascular events, and deaths are detailed. Adverse events are defined as any event reported after the start of study drug. Related adverse events are defined as any event reported after the start of study drug and considered by the Investigator to be possibly or probably related to study drug.

Safety data are generally presented for 3 different analysis datasets:

- All Postpartum and HUB Study Subjects: This dataset presents integrated safety data from the postpartum and HUB studies (VIT-11, VIT-01, VIT-09, and VIT-02/VIT-03) and from the postpartum or HUB subjects from Study VIT-06. This dataset represents anemic patients who are otherwise healthy and the indication for which approval is sought (1052 FCM exposed subjects).

- Oral Iron Controlled Studies: This dataset presents integrated data from trials (VIT-11, VIT-01, VIT-09, VIT-02/VIT-03, VIT-04, and CL-08) with comparable drug exposure to the primary efficacy studies and includes populations with high comorbidity, NDD-CKD and IBD (1057 FCM exposed subjects).

- Iron Sucrose Controlled Studies: This dataset presents integrated data from 2 trials (CL-15 and CARS) comparing FCM to another approved intravenous iron preparation as well as providing information regarding treatment in populations with relative high co-morbidity (149 FCM exposed subjects).

The Oral Iron Controlled and Iron Sucrose Controlled datasets, while informative, include data outside the targeted population. Other presentations include long-term data from the 44-week extension study, which was excluded from integration due to differences in study design, and data from all multicenter trials excluding the extension study, where applicable.

2.6.1 All Postpartum/HUB Studies (Target Population)

2.6.1.1 All Adverse Events

The overall incidence of adverse events was similar between the FCM (47.5%) and oral iron groups (53.1%) in the postpartum/HUB studies (**Table 39**). The incidence of gastrointestinal disorders was higher in the oral iron group (29.9%) compared to the FCM group (11.9%), while the incidence of adverse events associated with skin and subcutaneous tissue disorders was higher in the FCM group (6.6%) compared to the oral iron group (2.5%), which is consistent with the route of administration for each product.

Notable differences between the treatment groups were that a greater proportion of subjects in the oral iron group than the FCM group experienced constipation (12.9% vs. 2.3%) and nausea (8.1% vs. 2.3%) and a greater proportion of FCM subjects experienced blood phosphate decreased (3.4%) than oral iron subjects (0%). The difference in the incidence of gastrointestinal disorders is expected given the known effects of treatment with oral iron.

Among the postpartum/HUB subjects who were treated in the placebo-controlled, single-dose, crossover safety study (VIT-06), the most frequently experienced adverse event after receiving either FCM or placebo was headache (FCM: 5.0%; placebo: 3.0%).

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Table 39. Most Common Adverse Events (≥ 2.0% in Any Group) by System Organ Class, Preferred Term, and Treatment Group (All Postpartum and HUB Study Subjects)

			Crossover Safety Study[a]	
SOC **Preferred Term**	**FCM** **(N=773)**	**Oral Iron** **(N=668)**	**FCM** **(N=279)**	**Placebo** **(N=263)**
At Least 1 Adverse Event	367 (47.5%)	355 (53.1%)	66 (23.7%)	36 (13.7%)
Gastrointestinal disorders	92 (11.9%)	200 (29.9%)	15 (5.4%)	11 (4.2%)
Abdominal pain	20 (2.6%)	13 (1.9%)	2 (0.7%)	0
Constipation	18 (2.3%)	86 (12.9%)	3 (1.1%)	2 (0.8%)
Diarrhoea	12 (1.6%)	25 (3.7%)	1 (0.4%)	3 (1.1%)
Nausea	18 (2.3%)	54 (8.1%)	7 (2.5%)	4 (1.5%)
Vomiting	7 (0.9%)	17 (2.5%)	0	0
Infections and infestations	108 (14.0%)	90 (13.5%)	9 (3.2%)	11 (4.2%)
Nasopharyngitis	18 (2.3%)	21 (3.1%)	3 (1.1%)	2 (0.8%)
Investigations	52 (6.7%)	27 (4.0%)	4 (1.4%)	2 (0.8%)
Alanine aminotransferase increased	11 (1.4%)	15 (2.2%)	2 (0.7%)	0
Blood phosphate decreased	26 (3.4%)	0	1 (0.4%)	0
Nervous system disorders	110 (14.2%)	84 (12.6%)	22 (7.9%)	12 (4.6%)
Dizziness	20 (2.6%)	15 (2.2%)	4 (1.4%)	1 (0.4%)
Headache	77 (10.0%)	61 (9.1%)	14 (5.0%)	8 (3.0%)
Skin and subcutaneous tissue disorders	51 (6.6%)	17 (2.5%)	9 (3.2%)	2 (0.8%)
Rash	17 (2.2%)	9 (1.3%)	3 (1.1%)	0

Includes Studies VIT-11, VIT-01, VIT-09, VIT-02/VIT-03, and VIT-06.
a Incidence of adverse events limited to each 7 day study period (FCM vs. placebo).

A complete table presenting all adverse events by system organ class and preferred term is presented in Appendix A (Table 5.2.1.1AC).

2.6.1.2 All Related Adverse Events

The overall incidence of drug-related adverse events in the postpartum/HUB studies was higher in the oral iron (26.5%) group compared to the FCM (19.7%) group (**Table 40**). In the FCM group, the most common drug-related adverse events were headache (3.6%) and blood phosphate decreased (3.2%). In the oral iron group, the most common drug-related adverse events were constipation (11.4%), nausea (6.4%), diarrhea (2.8%), and headache (2.5%). Notable differences between the groups were for the greater incidence of drug-related gastrointestinal disorders in the oral iron group compared to the FCM group (22.9% vs. 5.4%) and the greater incidence of drug-related blood phosphate decreased in the FCM group compared to the oral iron group (3.2% vs. 0%).

Among the postpartum/HUB subjects who were treated in the placebo-controlled, single-dose, crossover safety study, headache (2.2%) was the most frequently experienced related adverse event after receiving FCM and nausea (1.1%) was the most frequently experienced related adverse event after receiving placebo.

Table 40. Most Common Drug-Related Adverse Events (≥ 2.0% in Any Group) by System Organ Class, Preferred Term, and Treatment Group (All Postpartum and HUB Study Subjects)

			Crossover Safety Study[a]	
SOC **Preferred Term**	**FCM** **(N=773)**	**Oral Iron** **(N=668)**	**FCM** **(N=279)**	**Placebo** **(N=263)**
At Least 1 Adverse Event	152 (19.7%)	177 (26.5%)	29 (10.4%)	10 (3.8%)
Gastrointestinal disorders	42 (5.4%)	153 (22.9%)	5 (1.8%)	5 (1.9%)
Constipation	14 (1.8%)	76 (11.4%)	0	0
Diarrhoea	4 (0.5%)	19 (2.8%)	0	2 (0.8%)
Nausea	12 (1.6%)	43 (6.4%)	3 (1.1%)	3 (1.1%)
Investigations	34 (4.4%)	13 (1.9%)	2 (0.7%)	2 (0.8%)
Blood phosphate decreased	25 (3.2%)	0	1 (0.4%)	0
Nervous system disorders	47 (6.1%)	24 (3.6%)	11 (3.9%)	4 (1.5%)
Headache	28 (3.6%)	17 (2.5%)	6 (2.2%)	2 (0.8%)

Includes Studies VIT-11, VIT-01, VIT-09, VIT-02/VIT-03, and VIT-06.

a Incidence of related adverse events limited to each 7 day study period (FCM vs. placebo).

2.6.1.3 Discontinuation of Study Drug Due to Adverse Events

In the postpartum and HUB studies, the overall incidence of adverse events resulting in premature discontinuation of study drug was 1.7% in the FCM group and 1.9% in the oral iron group (**Table 41**). Adverse events resulting in premature discontinuation of study drug experienced by 2 or more subjects were rash and urticaria in the FCM group and nausea, dizziness, diarrhea, and vomiting, in the oral iron group. All of the adverse events that led to premature discontinuation in FCM subjects were mild or moderate in severity and none were serious.

No adverse events resulted in premature discontinuation of study drug among postpartum/HUB subjects who were treated in the placebo-controlled, single-dose, crossover safety study.

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Table 41. Adverse Events Resulting in Premature Discontinuation of Study Drug Experienced by ≥ 2 Subjects in Any Group by System Organ Class, Preferred Term, and Treatment Group (All Postpartum and HUB Study Subjects)

			Crossover Safety Study	
SOC **Preferred Term**	**FCM (N=773)**	**Oral Iron (N=668)**	**FCM (N=279)**	**Placebo (N=263)**
At Least 1 Adverse Event	13 (1.7%)	13 (1.9%)	0	0
Gastrointestinal disorders	0	11 (1.6%)	0	0
Diarrhoea	0	2 (0.3%)	0	0
Nausea	0	7 (1.0%)	0	0
Vomiting	0	2 (0.3%)	0	0
Nervous system disorders	0	3 (0.4%)	0	0
Dizziness	0	3 (0.4%)	0	0
Skin and subcutaneous tissue disorders	7 (0.9%)	0	0	0
Rash	4 (0.5%)	0	0	0
Urticaria	2 (0.3%)	0	0	0

Includes Studies VIT-11, VIT-01, VIT-09, VIT-02/VIT-03, and VIT-06.

2.6.1.4 Serious Adverse Events

In the postpartum/HUB studies combined, the overall incidence of serious adverse events was 1.7% in the FCM group and 1.6% in the oral iron group (**Table 42**). Serious adverse events experienced by 2 subjects were uterine hemorrhage (0.3%) in the FCM group and endometritis (0.3%) and pelvic abscess (0.3%) in the oral iron group. No other specific serious adverse events were experienced by more than 1 subject. None of the serious adverse events experienced in the postpartum/HUB studies was considered related to study drug administration.

No serious adverse events were experienced among postpartum/HUB subjects who were treated in the placebo-controlled, single-dose, crossover safety study.

Table 42. Serious Adverse Events Experienced by ≥ 2 Subjects in Any Group by System Organ Class, Preferred Term, and Treatment Group (All Postpartum and HUB Study Subjects)

			Crossover Safety Study	
SOC **Preferred Term**	**FCM (N=773)**	**Oral Iron (N=668)**	**FCM (N=279)**	**Placebo (N=263)**
At Least 1 Adverse Event	13 (1.7%)	11 (1.6%)	0	0
Infections and infestations	6 (0.8%)	3 (0.4%)	0	0
Endometritis	0	2 (0.3%)	0	0
Pelvic abscess	0	2 (0.3%)	0	0
Reproductive system and breast disorders	3 (0.4%)	1 (0.1%)	0	0
Uterine haemorrhage	2 (0.3%)	1 (0.1%)	0	0

Includes Studies VIT-11, VIT-01, VIT-09, VIT-02/VIT-03, and VIT-06.

A complete table presenting all serious adverse events by system organ class and preferred term is presented in Appendix A (Table 5.2.1.2AC).

2.6.1.5 Deaths in Postpartum/HUB Studies

One death was reported among the 1052 postpartum/HUB subjects exposed to FCM in the trial program. No deaths were experienced among the oral iron subjects. The subject was a 27-year-old African-American female who received 1 dose of FCM 1000 mg 7 days after vaginal delivery. Eight days following dosing, the subject was found unresponsive in her home with frothy edema fluid from her mouth. Attempted resuscitation was unsuccessful. Autopsy findings indicated a dilated left ventricle, moderate pleural effusions, pulmonary edema, and soft tissue edema. The coroner reported the cause of death as peripartal cardiomyopathy with heart failure. The Investigator considered the event unrelated to study drug. A complete presentation of subjects who died in the FCM clinical program is detailed in Section 2.6.7.

2.6.1.6 Phosphate

Transient, asymptomatic decreases in serum phosphate were observed in both FCM and, to a lesser extent, oral iron subjects. The clinical significance of short-term mild-to-moderate hypophosphatemia (defined as serum phosphate values from 1.0 to <2.5 mg/dL) is not clear when observed in basically healthy individuals. Severe hypophosphatemia (defined as serum phosphate concentrations <0.9 mg/dL) is a marker of poor outcomes in severely ill patients, notably in the intensive care unit setting [57,58] although direct causal linkage to any particular organ function, including cardiac performance, has not been established.[58] In the short term, circulating phosphate is important for bioenergetics and in the longer term for bone mineralization. Less than 1% of total body phosphate is distributed in the extracellular fluid and thus serum values are highly subject to reductions from redistribution to the intracellular space as may occur rapidly with post-feeding glycolysis or less abruptly from erythrocyte 2,3-diphosphoglycerate formation, which correlates with serum phosphate levels.[57]

Serum phosphate was measured before and after dosing with FCM in Studies VIT-11, VIT-01, and VIT-02/VIT-03 and statistically significant mean decreases from baseline in phosphate were observed in FCM subjects compared to oral iron subjects in each study. Serum phosphate was not measured in the Study VIT-09 performed earlier in Europe.

A potentially clinically significant decrease in phosphate was prospectively defined as a "Common Terminology Criteria for Adverse Events", CTCAE grade 3 or 4 value **(Table 43)** observed after dosing for subjects whose baseline phosphate was within the laboratory reference range. The number of subjects identified with this definition can differ from the number of adverse event reports of decreased phosphate, because per protocol, Investigators were to record laboratory values as adverse events if the value was abnormal and in their judgment represented a clinically significant change from baseline.

Table 43. CTCAE v3.0 Criteria for Phopsphate, Serum-Low Adverse Events

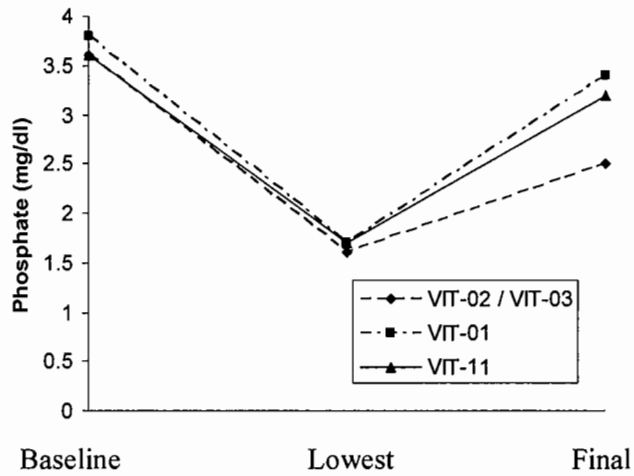
	CTCAE Grade			
Adverse Event	**1**	**2**	**3**	**4**
Phosphate, Serum-Low (hypophosphatemia)	<LLN – 2.5 mg/dl[1]	<2.5 – 2.0 mg/dl	<2.0 – 1.0 mg/dl	<1.0 mg/dl

[1] Lower Limit of Normal (LLN) varies by reference lab. The laboratory normal range for phosphate was 2.2 to 5.1 mg/dL in the HUB study and 2.4 to 4.9 mg/dL in the 2 postpartum studies.

Potentially Clinically Significant Values

Mean serum phosphate values, for subjects with potentially clinically significant abnormal phosphates; before FCM, at lowest value following FCM, and at final measurement in Studies VIT-11, VIT-01, and VIT-02/VIT-03 are shown in **Figure 8**.

Figure 8. Mean Serum Phosphate values for Subjects with Potentially Clinically Significant Serum Phosphates; Before FCM, at Lowest Value Following FCM, and at Final Measurement



The incidence of potentially clinically significant abnormal serum phosphate is shown in **Table 44**. Substantial differences in the incidence of serum phosphate values (< 2 g/dL) were observed among the studies. All of the laboratory values were CTCAE grade 3 with the exception of one CTCAE grade 4 value of 0.9 g/dL with no associated adverse events in Study VIT-02/VIT-03. No subject in any study achieved a serum phosphate level lower than 0.9 g/dL. No subject reported an adverse event that was judged to be possibly or probably related to decreased serum phosphate and no subject discontinued study drug due to decreased serum phosphate. The reports of blood phosphate decrease in the adverse event tables were asymptomatic events representing only the phosphate decrease.

Table 44. Incidence of Potentially Clinically Significant Abnormal Serum Phosphate in Studies VIT-11, VIT-01, and VIT-02/VIT-03

	n/N (%)	
Study	**FCM**	**Oral iron**
VIT-11 Postpartum	12/142 (8.5%)	0/147
VIT-01 Postpartum	14/174 (8.0%)	0/178
VIT-02/VIT-03 HUB	157/224 (70.1%)	0/219

n = number of subjects with baseline normal value reaching serum phosphate nadir < 2 g/dL (CTCAE Grade 3 or 4), N = total number of subjects with baseline normal phosphate

The median number of days to lowest phosphate after FCM dosing was approximately 2 weeks in Studies VIT-11, VIT-01, and VIT-02/VIT-03. Based on Kaplan-Meier estimates, the median number of days from lowest phosphate to recovery was 18 days in Study VIT-02/VIT-03 and 14 days in Study VIT-01. Similar findings were observed in Study VIT-11. Estimation of these time courses is limited by the protocol-specified schedule of assessment. In pharmacokinetic studies, the decrease in phosphate was not immediate but a trend downward was detectable after 24 hours (serum phosphate 4.0 $\pm$ 0.7 mg/dl pre-infusion versus 3.6 $\pm$ 0.8 mg/dl 24 hours post-infusion; n, 8; $p<0.01$).

Of the adverse events experienced by the 47 subjects (2 postpartum/45 HUB) whose phosphate dropped below 1.5 mg/dL, the only events potentially caused by a decreased phosphate level were fatigue (4 subjects). Two of the cases of fatigue occurred on study day 0, prior to phosphate decrease. The third fatigue case was CTCAE 1 (mild) occurring at the time the phosphate was 1.8 and resolved when the phosphate was 1.3. The fourth fatigue case was CTCAE 2 (moderate) and occurred with a phosphate of 2.1 mg/dL. Other adverse events experienced by > 2 subjects included injection site reactions (3 subjects) and headache (5 subjects).

Stratification of Adverse Events by Lowest Phosphate

When all adverse events occurring during the studies were summarized by lowest observed phosphate (≥2.5 mg/dL, 2 - <2.5 mg/dL, 1.5 - <2 mg/dL, <1.5 mg/dL) for the FCM group in Studies VIT-11 and VIT-01 combined, no clinically meaningful differences were observed among the phosphate groups for the overall proportion of subjects with adverse events. However, a greater proportion of subjects with lowest phosphate ≥2.5 mg/dL (15%) experienced headache, but this was not observed in subjects with nadir phosphates of 2 - <2.5 mg/dL (5.9%), 1.5 - <2 mg/dL (4%), or <1.5 mg/dL (0%).

The incidence of serious adverse events was also stratified by the lowest observed phosphate. When serious adverse events were presented by lowest phosphate (≥2.5 mg/dL, 2 - <2.5 mg/dL, 1.5 - <2 mg/dL, <1.5 mg/dL) for the FCM group in the postpartum studies (VIT-11 and VIT-01) combined (**Table 45**), no clinically meaningful differences were observed among the phosphate groups for the overall proportion of subjects with serious adverse events or for the proportion of subjects with any specific serious adverse events. No clinically meaningful difference from the oral iron group was observed.

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Table 45. Incidence of Serious Adverse Events Stratified by the Lowest Observed Value of Serum Phosphate (Postpartum Studies VIT-11 and VIT-01)

Preferred Term	FCM Subjects Phosphate Nadir (mg/dL)				Oral Iron (N = 325)
	≥2.5 (N = 213)	2 - <2.5 (N = 68)	1.5 - <2 (N = 25)	<1.5 (N = 2)	
≥1 Serious Adverse Event	3 (1.4%)	3 (4.8%)	0	0	8 (2.5%)
Cardiac failure congestive	0	0	0	0	1 (0.3%)
Haemorrhoids	1 (0.5%)	0	0	0	0
Cholecystitis	0	1 (1.5%)	0	0	0
Cholecystitis acute	1 (0.5%)	0	0	0	0
Cholelithiasis	0	0	0	0	1 (0.3%)
Appendicitis	0	1 (1.5%)	0	0	0
Endometritis	0	0	0	0	2 (0.6%)
Pelvic abscess	0	0	0	0	2 (0.6%)
Postoperative infection	1 (0.5%)	0	0	0	0
Pyelonephritis	0	1 (1.5%)	0	0	0
Major depression	0	0	0	0	1 (0.3%)
Pulmonary embolism	0	0	0	0	1 (0.3%)
Thrombophlebitis	0	0	0	0	1 (0.3%)

1 Includes all subjects with a postdose phosphate measurement, regardless of phosphate value at baseline.
2 Subjects stratified by lowest phosphate nadir observed during trial.

When adverse events and serious adverse events were presented by lowest observed phosphate (≥2.5 mg/dL, 2 - <2.5 mg/dL, 1.5 - <2 mg/dL, <1.5 mg/dL) for the FCM group in the HUB study (VIT-02/VIT-03), no clinically meaningful differences were observed among phosphate groups for the overall proportion of subjects with adverse events or serious adverse events or for the proportion of subjects with any specific adverse event or serious adverse event. No clinically meaningful difference from the oral iron group was observed. A summary of the incidence of serious adverse events stratified by the lowest observed value of serum phosphate in Study VIT-02/VIT-03 is presented in **Table 46**.

Table 46. Incidence of Serious Adverse Events Stratified by the Lowest Observed Value of Serum Phosphate (HUB Study VIT-02/VIT-03)

Preferred Term	FCM Subjects Phosphate Nadir (mg/dL) ≥2.5 (N = 21)	2 - <2.5 (N = 47)	1.5 - <2 (N = 115)	<1.5 (N = 45)	Oral Iron (N = 226)
≥1 Serious Adverse Event	0	2 (4.3%)	1 (0.9%)	0	3 (1.3%)
Abdominal pain	0	0	0	0	1 (0.4%)
Chest pain	0	1 (2.1%)	0	0	0
Pelvic inflammatory disease	0	0	1 (0.9%)	0	0
Uterine leiomyoma	0	0	0	0	1 (0.4%)
Transient ischaemic attack	0	0	0	0	1 (0.4%)
Uterine hemorrhage	0	1 (2.1%)	0	0	1 (0.4%)

1 Includes all subjects with a postdose phosphate measurement, regardless of phosphate value at baseline.
2 Subjects stratified by lowest phosphate nadir observed during trial.

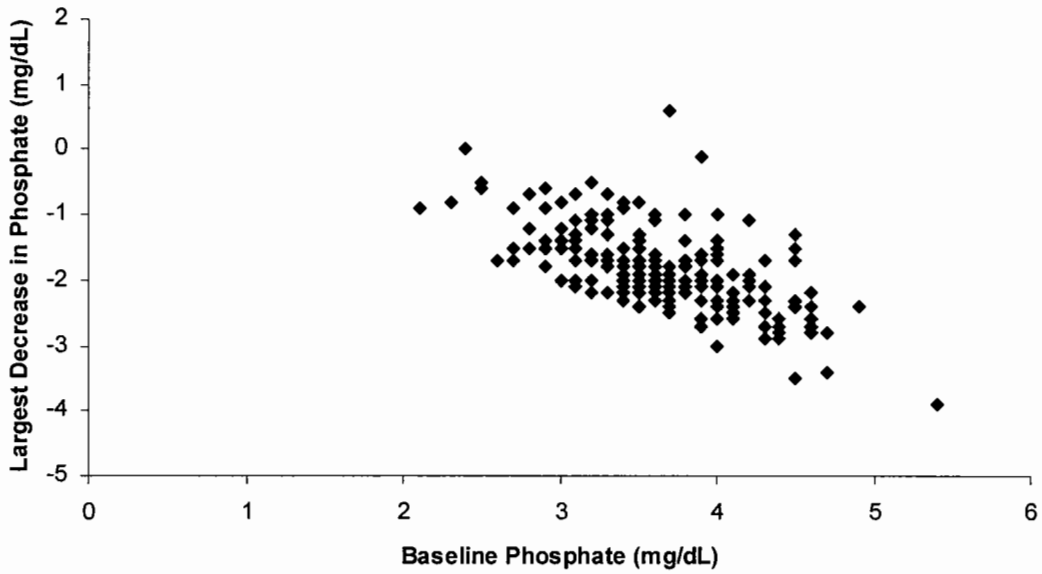
Relevant Additional Clinical Data

Baseline phosphate, changes in calcium and magnesium, increase in hemoglobin, cause of anemia, and urinary excretion were examined for possible relationships to the transient decrease in phosphate. Results discussed below, suggested that multiple processes may be responsible.

Baseline Phosphate

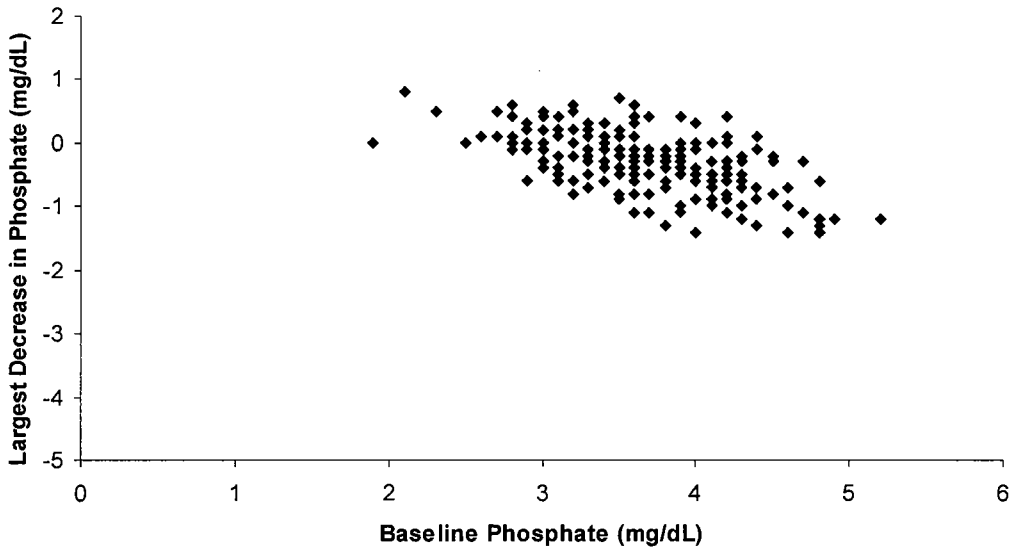
Baseline serum phosphate was a statistically significant predictor of change to lowest observed phosphate using linear regression in HUB Study VIT-02/VIT-03. The Pearson correlation of baseline serum phosphate with change in serum phosphate was –0.630 (**Figure 9**). Thus, higher baseline serum phosphate values were associated with larger decreases in serum phosphate post treatment.

Figure 9. Summary of the Largest Decreases in Phosphate Values by Baseline Values in the FCM Group (HUB Study VIT-02/VIT-03)



In order to evaluate whether the observed relationship between baseline and lowest serum phosphate was specific to FCM, the relationship was also evaluated for oral iron. Pearson's correlation was –0.585 for oral iron (**Figure 10**).

Figure 10. Summary of the Largest Decreases in Phosphate Values by Baseline Values in the Oral Iron Group (HUB Study VIT-02/VIT-03)



The relation between baseline and change in serum phosphate was also assessed in Studies VIT-11 and VIT-01 in order to confirm the observation in Study VIT-02/VIT-03. Statistically significant negative correlation was again observed for both FCM and oral iron. The relationship between baseline and change in serum phosphate was also assessed in another study of FCM (Study VIT-04) in order to confirm that the NDD-CKD population was consistent with the postpartum and HUB populations. Statistically significant negative correlation of change in phosphate with baseline phosphate was again observed for both FCM and oral iron. The low values were transient and did not result in any adverse events. The lowest phosphate reached during the NDD-CKD study was 1.7 mg/dL.

The majority of both the FCM and oral iron-treated subjects had a post-baseline decrease in phosphate. The fact that the majority of oral iron-treated subjects also had a decrease in phosphate and the documented negative correlation of baseline serum phosphate with changes in serum phosphate for both the FCM and oral iron treatment groups suggest that the mechanism may be intrinsic to iron therapy in this severely anemic population.

Changes in Calcium and Magnesium

In Studies VIT-11, VIT-01, and VIT-02/VIT-03, no clinically meaningful changes from baseline in serum calcium values were observed (**Table 47**). In addition, serum magnesium values were measured in Study VIT-11, which also showed no clinically meaningful change from baseline.

Table 47. Mean Changes From Baseline to Day 42 in Serum Calcium and Magnesium Values (Studies VIT-11, VIT-01, and VIT-02/VIT-03)

	FCM		Oral Iron		
	N	Change to Day 42 (SD)	N	Change to Day 42 (SD)	P-value
Study VIT-11					
Calcium (mg/dL)	137	0.7 (0.50)	143	0.6 (0.45)	0.2858
Magnesium (mg/dL)	129	0.1 (0.18)	139	0.1 (0.18)	07894
Study VIT-01					
Calcium (mg/dL)	164	0.7 (0.54)	162	0.07 (0.49)	0.5930
Study VIT-02/VIT-03					
Calcium (mg/dL)	228	-0.04 (0.403)	225	0.09 (0.377)	<0.001

Note: serum magnesium values were not measured in Studies VIT-01 and VIT-02/VIT-03.

Hemoglobin Increase

The decreases in serum phosphate at 14 days after FCM infusion had a weak correlation with the increase in hemoglobin at 14 days (Pearson correlation = 0.259) that was not observed with oral iron (Pearson correlation = 0.087).

Cause of Anemia

Subjects in postpartum Study VIT-11 had a mean baseline phosphate of 4.2 mg/dl compared to a mean baseline of 3.7 mg/dl in HUB Study VIT-02/VIT-03 (**Table 48**). For the 12 subjects in post-partum Study VIT-11 who developed a potentially clinically significant phosphate value, the mean at baseline was 3.6 ± 0.5 mg/dl. This was similar to the mean baseline phosphate value (3.6 mg/dl) in HUB Study VIT-02/VIT-03 for subjects with a potentially clinically significant phosphate value.

Table 48. Mean Baseline Phosphate for All Subjects and Subjects with a Potentially Clinially Significant (PCS) Phosphate Value After Dosing in Studies VIT-01, VIT-11, and VIT-02/VIT-03

		FCM	
Study	**Subjects**	**N**	**Mean (SD)**
VIT-01	All	174	4.2 (0.6)
Postpartum	Subjects with a PCS Phosphate value	14	3.8 (0.5)
VIT-11	All	142	4.2 (0.6)
Postpartum	Subjects with a PCS Phosphate value	12	3.6 (0.5)
VIT-02/VIT-03	All	230	3.7 (0.5)
HUB	Subjects with a PCS Phosphate value	157	3.6 (0.5)

Urinary Excretion

Analytes possibly related to urinary excretion of phosphate were measured before and after dosing with FCM in Study VIT-11. No statistically significant differences were observed between the treatment groups for mean change from baseline to Day 42 in renal phosphate/creatinine ratio (phosphate clearance), tubular reabsorption of phosphate, microalbumin/creatinine ratio or glucosuria. There was a slight decrease in tubular reabsorption

of phosphate from an average baseline value of 92.6% to 88.7% at day 14, and recovery to 91.2 and 91.4% at days 28 and 42, respectively. Although fluctuating, all of these values are within the normal range. There was no change in phosphate clearance or evidence of more global renal tubule dysfunction such as glucosuria or microalbuminuria at any visit. A summary of the mean changes from baseline to Day 42 in urinalysis parameters is presented in **Table 49**.

Table 49. Mean Changes From Baseline to Day 42 in Urinalysis Parameters (Study VIT-11)

	FCM			Oral Iron			
Urinalysis Parameter (Units)	**N**	**Baseline Mean (SD)**	**Change to Day 42 (SD)**	**N**	**Baseline Mean (SD)**	**Change to Day 42 (SD)**	**p-value**
Tubular Reabsorption Rate of Phosphate (%)	131	92.6 (3.23)	-1.0 (5.33)	134	91.8 (4.18)	0.0 (4.75)	0.1026
Urine Microalbumin/ Creatinine Ratio (mg/gm)	130	76.36 (179.60)	-57.6 (163.23)	134	103.1 (228.56)	-15.3 (548.98)	0.3998
Urine Phosphate/ Urine Creatinine Ratio (%)	131	0.467 (0.2140)	-0.025 (0.3181)	134	0.506 (0.2269)	-0.067 (0.2899)	0.2572

Discussion

To summarize, decreases in serum phosphate following FCM treatment:

- are transient, resolving over an average of 18 days
- have slow onset with maximum declines at 14 days
- occur commonly, with a high incidence in the HUB population
- are asymptomatic with no adverse effect of lower post-treatment values on the adverse event or serious adverse event rate and
- are not associated with other electrolyte changes.

There may be multiple mechanisms for the observed decrease in phosphate. Phosphate decreases are associated with RBC formation with decreases also noted in oral iron treated subjects and with slight reductions in the renal reabsorption of phosphate without clinical evidence of global renal tubule dysfunction. Regardless of potential mechanisms, the effects of FCM on serum phosphate are notably transient and without clinical significance in the population for which an indication is sought.

The lower baseline and post-infusion serum phosphate values in the HUB subjects presumably relate to the greater chronicity of their disease relative to the post-partum patients, and potentially to their greater degree of erythropoiesis. The absence of other electrolyte abnormalities, that it occurred in the most iron deficient population (HUB), coupled with previous information that serum phosphate levels fall at the onset of hemolytic anemia,[59] during recovery from aplastic crisis associated with hereditary spherocytosis,[60] and during reconstitution of hematopoiesis after allogeneic peripheral blood stem cell transplantation,[61] suggests that the resultant

hypophosphatemia may be in part, a physiologic consequence of increased cellular demand for phosphate during acute acceleration of erythropoiesis. Studies in the literature with saccharated ferric oxide (Fesin, Japan, not available in the US) demonstrate a transient increase in renal phosphate clearance.[62] This iron product is chemically uncharacterized with dosing characteristics much different than available IV irons in the US.

Phosphate experts who have reviewed this data consider the decrease in phosphate to be interesting but clinically not important in the postpartum and heavy uterine bleeding populations. They recommend that patients with any clinical evidence of malnutrition/alcoholism or other risks for hypophosphatemia have serum phosphate concentrations measured on the day of FCM infusion and, if low, receive instructions to take skim milk (dietary) or phosphate supplements (for 1-2 weeks).

Conclusion

Transient, asymptomatic decreases in serum phosphate were observed in both FCM and oral iron subjects, but the decreases did not result in symptomatic adverse events or serious adverse events. Relevant additional clinical data suggested that multiple processes may be responsible. Phosphate experts recommend that patients with a likelihood of baseline hypophosphatemia have serum phosphate measured on the day of FCM infusion and take appropriate dietary supplements if low.

2.6.2 Oral Iron Controlled Studies

Oral iron controlled studies included the low risk postpartum and HUB populations as well as the high risk NDD-CKD and IBD populations.

2.6.2.1 All Adverse Events

A statistically significant difference was observed between the FCM (48.2%) and oral iron groups (53.1%) in the oral iron controlled studies for the overall incidence of adverse events ($p = 0.0332$; **Table 50**). The incidence of gastrointestinal disorders was statistically significantly ($p<0.0001$) higher in the oral iron group (31.2%) compared to the FCM group (13.3%), while the incidences of adverse events associated with laboratory investigations and skin and subcutaneous tissue disorders were statistically significantly higher in the FCM group (7.0% and 6.6%, respectively) compared to the oral iron group (3.7% and 2.4%, respectively).

Among the gastrointestinal disorders, greater proportions of subjects in the oral iron group than the FCM group experienced constipation (12.6% vs. 1.9%), nausea (7.4% vs. 2.2%), diarrhoea (4.0% vs. 1.5%), and vomiting (2.5% vs. 0.9%), while a greater proportion of FCM subjects (2.6%) experienced abdominal pain than oral iron subjects (1.9%). Among the adverse events associated with laboratory investigations, a greater proportion of FCM subjects experienced blood phosphate decreased (2.5%) than oral iron subjects (0%). Among the adverse events associated with skin and subcutaneous tissue disorders, a greater proportion of FCM subjects experienced rash (2.1%) than oral iron subjects (1.2%).

Table 50. Most Common Adverse Events (≥2.0% in Either Group) by System Organ Class, Preferred Term, and Treatment Group (Oral Iron Controlled 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%)	

Includes Studies VIT-11, VIT-01, VIT-09, VIT-02/VIT-03, VIT-04, and CL-08.

The incidence of adverse events associated with general disorders and administration site conditions was also statistically significantly (p<0.0001) higher in the FCM group (11.0%) compared to the oral iron group (4.4%). This difference was primarily related to adverse events of the infusion or injection site of study drug administration, which were not observed among subjects receiving oral iron.

A complete table presenting all adverse events by system organ class and preferred term is presented in Appendix A (Table 5.1.1.3).

2.6.2.2 All Related Adverse Events

The overall incidence of drug-related adverse events in the oral iron controlled studies was higher in the oral iron (26.1%) group compared to the FCM (18.4%) group (**Table 51**). In the FCM group, the most common drug-related adverse events were headache (3.0%) and blood phosphate decreased (2.4%). In the oral iron group, the most common drug-related adverse events were constipation (11.3%), nausea (5.8%), diarrhea (3.0%), and headache (2.2%). Notable differences between the groups were for the greater incidence of drug-related gastrointestinal disorders in the oral iron group compared to the FCM group (23.0% vs. 4.7%) and the greater incidence of blood phosphate decreased in the FCM group compared to the oral iron group (2.4% vs. 0%).

Table 51. Most Common Drug-Related Adverse Events (≥ 2.0% in Either Group) by System Organ Class, Preferred Term, and Treatment Group (Oral Iron Controlled Studies)

SOC Preferred Term	FCM (N=1057)	Oral Iron (N=834)
At Least 1 Adverse Event	195 (18.4%)	218 (26.1%)
Gastrointestinal disorders	50 (4.7%)	192 (23.0%)
Constipation	14 (1.3%)	94 (11.3%)
Diarrhoea	6 (0.6%)	25 (3.0%)
Nausea	15 (1.4%)	48 (5.8%)
Investigations	47 (4.4%)	13 (1.6%)
Blood phosphate decreased	25 (2.4%)	0
Nervous system disorders	52 (4.9%)	25 (3.0%)
Headache	32 (3.0%)	18 (2.2%)

Includes Studies VIT-11, VIT-01, VIT-09, VIT-02/VIT-03, VIT-04, and CL-08.

2.6.2.3 Discontinuation of Study Drug Due to Adverse Events

In the oral iron controlled studies, the overall incidence of adverse events resulting in premature discontinuation of study drug was 1.6% in the FCM group and 3.0% in the oral iron group (**Table 52**). Among the adverse events that led to premature discontinuation of study drug, the incidence of gastrointestinal disorders was higher in the oral iron group (2.4%) compared to the FCM group (0.1%), while the incidence of adverse events associated with skin and subcutaneous tissue disorders were higher in the FCM group (0.8%) compared to the oral iron group (0%).

Table 52. Adverse Events Resulting in Premature Discontinuation of Study Drug Experienced by ≥ 2 Subjects in Any Group by System Organ Class, Preferred Term, and Treatment Group (Oral Iron Controlled Studies)

SOC Preferred Term	FCM (N=1057)	Oral Iron (N=834)
At Least 1 Adverse Event	17 (1.6%)	25 (3.0%)
Gastrointestinal disorders	1 (0.1%)	20 (2.4%)
Abdominal pain upper	0	2 (0.2%)
Colitis Ulcerative	0	2 (0.2%)
Constipation	0	2 (0.2%)
Diarrhoea	0	5 (0.6%)
Gastrointestinal haemorrhage	0	2 (0.2%)
Nausea	0	7 (0.8%)
Vomiting	0	3 (0.4%)
General disorders and administration site conditions	6 (0.6%)	1 (0.1%)
Infusion Site Reaction	2 (0.2%)	0
Nervous system disorders	0	3 (0.4%)
Dizziness	0	3 (0.4%)
Skin and subcutaneous tissue disorders	8 (0.8%)	0
Rash	4 (0.4%)	0
Urticaria	2 (0.2%)	0

Includes Studies VIT-11, VIT-01, VIT-09, VIT-02/VIT-03, VIT-04, and CL-08.

2.6.2.4 Serious Adverse Events

In the oral iron controlled studies, the overall incidence of serious adverse events was 3.2% in the FCM group and 2.5% in the oral iron group (**Table 53**). Serious adverse events experienced by 2 or more subjects were cardiac failure congestive, coronary artery disease, sepsis, and uterine haemorrhage in the FCM group and cardiac failure congestive, gastrointestinal haemorrhage, endometritis, pelvic abscess, and renal failure chronic in the oral iron group.

Table 53. Serious Adverse Events Experienced by ≥ 2 Subjects in Any Group by System Organ Class, Preferred Term, and Treatment Group (Oral Iron Controlled Studies)

SOC Preferred Term	FCM (N=1057)	Oral Iron (N=834)
At Least 1 Serious Adverse Event	34 (3.2%)	21 (2.5%)
Cardiac disorders	9 (0.9%)	3 (0.4%)
Cardiac failure congestive	2 (0.2%)	2 (0.2%)
Coronary artery disease	2 (0.2%)	0
Gastrointestinal disorders	6 (0.6%)	4 (0.5%)
Gastrointestinal haemorrhage	1 (0.1%)	2 (0.2%)
Infections and infestations	10 (0.9%)	3 (0.4%)
Endometritis	0	2 (0.2%)
Pelvic abscess	0	2 (0.2%)
Sepsis	2 (0.2%)	0
Renal and urinary disorders	0	3 (0.4%)
Renal failure chronic	0	2 (0.2%)
Reproductive system and breast disorders	3 (0.3%)	1 (0.1%)
Uterine haemorrhage	2 (0.2%)	1 (0.1%)

Includes Studies VIT-11, VIT-01, VIT-09, VIT-02/VIT-03, VIT-04, and CL-08.

None of the serious adverse events experienced in the oral iron controlled studies was considered related to study drug administration.

2.6.2.5 Deaths in Oral Iron Controlled Studies

Four deaths by 4 different mechanisms were reported among the 1057 subjects exposed to FCM in the oral iron controlled studies; 1 in Study VIT-01 (postpartum cardiomyopathy), 2 in Study VIT-04 (motor vehicle accident and urosepsis/hospice care), and 1 in Study CL-08 (witnessed arrest). None of the deaths was considered related to treatment by the Investigator. No deaths were experienced among the oral iron subjects. A complete presentation of subjects who died in the FCM clinical program is detailed in Section 2.6.7.

2.6.3 Iron Sucrose Controlled Studies

Iron sucrose controlled studies included the high-risk HD and CHF populations.

One of the iron sucrose controlled studies (CARS) also contained placebo subjects for both the FCM and iron sucrose treatment arms. There were 15 placebo subjects dosed in this study. Given the small number of placebo subjects in relation to the FCM and iron sucrose treatment groups, they have been removed from the data displays.

2.6.3.1 All Adverse Events

The overall incidence of adverse events was similar between the FCM (44.3%) and iron sucrose groups (40.0%) in the iron sucrose controlled studies (**Table 54**). Notable differences between the treatment groups were for the incidences of gastrointestinal disorders and nervous system disorders, which were higher in the iron sucrose group (7.6% and 8.3%, respectively) compared to the FCM group (3.4% and 2.0%, respectively).

Table 54. Most Common Adverse Events (≥ 2.0% in Any Group) by System Organ Class, Preferred Term, and Treatment Group (Iron Sucrose Controlled Studies)

SOC Preferred Term	FCM (N=149)	Iron Sucrose (N=145)
At Least 1 Adverse Event	66 (44.3%)	58 (40.0%)
Cardiac disorders	8 (5.4%)	10 (6.9%)
Cardiac failure	1 (0.7%)	3 (2.1%)
Tachycardia	3 (2.0%)	1 (0.7%)
Gastrointestinal disorders	5 (3.4%)	11 (7.6%)
Vomiting	1 (0.7%)	3 (2.1%)
General disorders and administration site conditions	6 (4.0%)	7 (4.8%)
Asthenia	0	3 (2.1%)
Infections and infestations	13 (8.7%)	12 (8.3%)
Nasopharyngitis	3 (2.0%)	0
Injury, poisoning and procedural complications	8 (5.4%)	6 (4.1%)
Medical device complication	3 (2.0%)	1 (0.7%)
Metabolism and nutrition information	9 (6.0%)	6 (4.1%)
Hyperkalaemia	4 (2.7%)	3 (2.1%)
Hypoglycaemia	3 (2.0%)	0
Musculoskeletal and connective tissue disorders	10 (6.7%)	12 (8.3%)
Arthralgia	1 (0.7%)	3 (2.1%)
Muscle cramp	6 (4.0%)	5 (3.4%)
Nervous system disorders	3 (2.0%)	12 (8.3%)
Headache	3 (2.0%)	6 (4.1%)
Skin and subcutaneous tissue disorders	3 (2.0%)	3 (2.1%)
Pruritus	1 (0.7%)	3 (2.1%)
Vascular disorders	24 (16.1%)	29 (20.0%)
Hypertension	9 (6.0%)	14 (9.7%)
Hypotension	12 (8.1%)	12 (8.3%)

Includes Studies CL-15 and CARS.

2.6.3.2 All Related Adverse Events

The overall incidence of drug-related adverse events in the iron sucrose controlled studies was numerically higher in the iron sucrose (11.0%) group compared to the FCM (5.4%) group (**Table 55**). Drug-related events of hypotension and hypertension were experienced by 3.4% and 2.1% of iron sucrose subjects, while no specific drug-related adverse event was experienced by at least 2% of FCM subjects.

Table 55. Most Common Drug-Related Adverse Events (≥ 2.0% in Any Group) by System Organ Class, Preferred Term, and Treatment Group (All Iron Sucrose Controlled Studies)

SOC Preferred Term	FCM (N=149)	Iron Sucrose (N=145)
At Least 1 Adverse Event	8 (5.4%)	16 (11.0%)
Vascular disorders	1 (0.7%)	8 (5.5%)
Hypertension	0	3 (2.1%)
Hypotension	1 (0.7%)	5 (3.4%)

Includes Studies CL-15 and CARS.

2.6.3.3 Discontinuation of Study Drug Due to Adverse Events

In the iron sucrose controlled studies, the overall incidence of adverse events resulting in premature discontinuation of study drug was 1.3% in the FCM group and 2.1% in the iron sucrose group (**Table 56**). The only event that led to premature discontinuation of study drug in at least 2 subjects was gastrointestinal hemorrhage and melena, which were both reported in iron sucrose subjects.

Table 56. Adverse Events Resulting in Premature Discontinuation of Study Drug by System Organ Class, Preferred Term, and Treatment Group (All Iron Sucrose Controlled Studies)

SOC Preferred Term	FCM (N=149)	Iron Sucrose (N=145)
At Least 1 Adverse Event	2 (1.3%)	3 (2.1%)
Gastrointestinal disorders	0	2 (1.4%)
Gastrointestinal haemorrhage	0	2 (1.4%)
Melaena	0	2 (1.4%)
Infections and infestations	1 (0.7%)	1 (0.7%)
Bacterial sepsis	1 (0.7%)	0
Febrile infection	0	1 (0.7%)
Pseudomonal sepsis	0	1 (0.7%)
Injury, poisoning and procedural complications	1 (0.7%)	0
Medical device complication	1 (0.7%)	0
Vascular disorders	0	1 (0.7%)
Hypotension	0	1 (0.7%)

Includes Studies CL-15 and CARS.

2.6.3.4 Serious Adverse Events

In the iron sucrose controlled studies, the overall incidence of serious adverse events was 6.0% in the FCM group and 9.0% in the iron sucrose group (**Table 57**). Serious adverse events experienced by 2 or more subjects were myocardial infarction (1.3%) in the FCM group and cardiac failure (2.1%), gastrointestinal hemorrhage (1.4%) and melena (1.4%) in the iron sucrose group. No other specific serious adverse events were experienced by more than 1 subject.

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Table 57. Serious Adverse Events by System Organ Class, Preferred Term, and Treatment Group (All Iron Sucrose Controlled Studies)

SOC Preferred Term	FCM (N=149)	Iron Sucrose (N=145)
At Least 1 Adverse Event	9 (6.0%)	13 (9.0%)
Cardiac disorders	4 (2.7%)	4 (2.8%)
Acute myocardial infarction	0	1 (0.7%)
Angina unstable	1 (0.7%)	0
Cardiac failure	1 (0.7%)	3 (2.1%)
Myocardial infarction	2 (1.3%)	0
Ventricular arrhythmia	0	1 (0.7%)
Gastrointestinal disorders	0	2 (1.4%)
Gastrointestinal haemorrhage	0	2 (1.4%)
Melaena	0	2 (1.4%)
General disorders and administration site conditions	1 (0.7%)	0
Catheter related complication	1 (0.7%)	0
Catheter site haemorrhage	1 (0.7%)	0
Infections and infestations	1 (0.7%)	2 (1.4%)
Bacterial sepsis	1 (0.7%)	0
Genitourinary tract Infection	0	1 (0.7%)
Lung infection	0	1 (0.7%)
Pseudomonal sepsis	0	1 (0.7%)
Injury, poisoning and procedural complications	1 (0.7%)	2 (1.4%)
Arteriovenous fistula site haemorrhage	0	1 (0.7%)
Arteriovenous fistula thrombosis	1 (0.7%)	1 (0.7%)
Musculoskeletal and connective tissue disorders	1 (0.7%)	0
Nodal arthritis	1 (0.7%)	0
Nervous system disorders	0	2 (1.4%)
Hypertensive encephalopathy	0	1 (0.7%)
Hypoglycaemic coma	0	1 (0.7%)
Surgical and medical procedures	2 (1.3%)	0
Arteriovenous fistula operation	1 (0.7%)	0
Renal transplant	1 (0.7%)	0
Vascular disorders	1 (0.7%)	4 (2.8%)
Arterial thrombosis limb	0	1 (0.7%)
Haematoma	1 (0.7%)	1 (0.7%)
Haemorrhage	0	1 (0.7%)
Hypotension	0	1 (0.7%)

Includes Studies CL-15 and CARS.

2.6.3.5 Deaths in Iron Sucrose Controlled Studies

In the iron sucrose controlled studies, 1 death was reported among the 149 subjects exposed to FCM (Study CL-15; myocardial infarction) and 1 death was reported among the 145 subjects exposed to iron sucrose (Study CARS; congestive heart failure). A complete presentation of subjects who died in the FCM clinical program is detailed in Section 2.6.7.

2.6.4 Long-Term Adverse Events

During the 44-week long-term extension study (Study VIT-05) conducted in NDD-CKD subjects, at least 1 adverse event was experienced by 66.1% (84/127) of subjects (**Table 58**). The most commonly (≥ 5%) experienced adverse events were oedema peripheral (7.1%), hypertension (6.3%), and urinary tract infection (5.5%).

Table 58. Adverse Events Experienced by ≥2% or More Subjects (Study VIT-05)

MedDRA SOC Preferred Term	FCM (N=127)
At Least One Adverse Event	84 (66.1%)
Gastrointestinal Disorders	20 (15.7%)
Constipation	3 (2.4%)
Diarrhoea	6 (4.7%)
Nausea	4 (3.1%)
General Disorders and Administration Site Conditions	26 (20.5%)
Fatigue	4 (3.1%)
Oedema	5 (3.9%)
Oedema peripheral	9 (7.1%)
Infections and Infestations	31 (24.4%)
Cellulitis	3 (2.4%)
Localized infection	4 (3.1%)
Nasopharyngitis	4 (3.1%)
Upper respiratory tract infection	5 (3.9%)
Urinary tract infection	7 (5.5%)
Metabolism and Nutrition Disorders	14 (11.0%)
Hyperlipidemia	3 (2.4%)
Hypoglycaemia	4 (3.1%)
Vitamin D deficiency	3 (2.4%)
Musculoskeletal and Connective Tissue Disorders	16 (12.6%)
Arthralgia	6 (4.7%)
Back pain	4 (3.1%)
Nervous System Disorders	16 (12.6%)
Dizziness	4 (3.1%)
Headache	5 (3.9%)
Psychiatric Disorders	3 (2.4%)
Depression	3 (2.4%)
Respiratory, Thoracic, and Mediastinal Disorders	20 (15.7%)
Cough	5 (3.9%)
Epistaxis	5 (3.9%)
Skin and Subcutaneous Tissue Disorders	18 (14.2%)
Rash	4 (3.1%)
Skin ulcer	6 (4.7%)
Vascular Disorders	12 (9.4%)
Hypertension	7 (5.5%)

At least 1 drug-related adverse event (defined as probably or possibly related) was experienced by 4.7% (6/127) of subjects. Drug-related adverse events included injection site discoloration (2 subjects), dizziness, infusion site pain, infusion site reaction, gastrointestinal infection, and hypotension (1 subject each).

During the study, 23 (18.1%) subjects, including 2 subjects who died (acute gastrointestinal bleeding and colonic perforation secondary to diverticulitis), experienced at least 1 serious adverse event during the study. None of the subjects reported serious adverse events during the study that were considered by the Investigator to be related to study drug. Six (6; 4.7%) subjects

were prematurely discontinued from study drug or the study due to the occurrence of adverse events. Each of these subjects experienced adverse events that were considered to have no relationship to study drug by the Investigator.

When adverse events were summarized by dose group, maximum hemoglobin, and hemoglobin change from baseline within 30 days after dosing, no clinically meaningful differences were observed for the overall proportion of subjects with adverse events or serious adverse events or for the proportion of subjects with any specific adverse events or serious adverse events.

Repeat course (cycle) safety data is available in the NDD-CKD randomized controlled study (VIT-04) and the 44 week long-term extension study (VIT-05). When adverse events and serious adverse events were presented by number of FCM courses received (1 course vs. 2 courses, 3 courses, 4 courses, 5 courses or ≥ 6 courses) for the NDD-CKD studies (VIT-04 and VIT-05) combined, no clinically meaningful differences were observed among the number of FCM courses for the overall proportion of subjects with adverse events/serious adverse events or for the proportion of subjects with any specific adverse events/serious adverse events. A summary of all adverse events by number of FCM courses received is presented in Appendix A (Table 8.3).

2.6.5 Adverse Event Analysis for Predictive Baseline Factors

The possible influence of FCM dosing on the incidence of adverse events and FCM dosing and maximum hemoglobin increase on the incidence of serious adverse events was examined and results are presented in the following section. The possible influence of decreased phosphate on the incidence of serious adverse events was also examined and the results are presented with an overview of the effect of FCM on phosphate in Section 2.6.1.6.

2.6.5.1 FCM Dose

No clear pattern of dose-response was observed for the incidence of adverse events or serious adverse events stratified by total dose of FCM in the oral iron controlled studies or HD studies (**Table 59** and **Table 60**, respectively).

Table 59. Incidence of Serious Adverse Events Stratified by Total Dose of FCM (Oral Iron Controlled Studies)

Population Preferred Term	Total Dose of FCM 0-1000 mg (N=166)	1001-1400 mg (N=429)	>1400 mg (N=462)
≥1 Serious Adverse Event	11 (6.6%)	10 (2.3%)	13 (2.8%)
Cardiac arrest	1 (0.6%)	0	0
Cardiac failure	1 (0.6%)	0	0
Cardiac failure congestive	1 (0.6%)	0	1 (0.2%)
Coronary artery disease	2 (1.2%)	0	0
Mitral valve prolapse	0	0	1 (0.2%)
Myocardial infarction	1 (0.6%)	0	0
Palpitations	1 (0.6%)	0	0
Tachycardia	0	1 (0.2%)	0
Colitis ulcerative	0	1 (0.2%)	0
Crohn's disease	0	1 (0.2%)	0
Gastrointestinal haemorrhage	0	1 (0.2%)	0
Haemorrhoids	0	1 (0.2%)	0
Pancreatitis acute	1 (0.6%)	0	0
Small intestinal haemorrhage	0	0	1 (0.2%)
Chest pain	0	0	1 (0.2%)
Pyrexia	0	1 (0.2%)	0
Autoimmune hepatitis	0	0	1 (0.2%)
Cholecystitis	0	0	1 (0.2%)
Cholecystitis acute	0	1 (0.2%)	0
Appendicitis	0	1 (0.2%)	0
Cellulitis	0	0	1 (0.2%)
Endometritis decidual	0	1 (0.2%)	0
Pelvic inflammatory disease	1 (0.6%)	0	0
Postoperative infection	0	0	1 (0.2%)
Pyelonephritis	0	1 (0.2%)	0
Sepsis	1 (0.6%)	1 (0.2%)	0
Skin infection	0	0	1 (0.2%)
Upper respiratory tract infection	1 (0.6%)	0	0
Polytraumatism	0	0	1 (0.2%)
Postoperative fever	0	0	1 (0.2%)
Electrolyte depletion	0	0	1 (0.2%)

Includes Studies VIT-11, VIT-01, VIT-09, VIT-02/VIT-03, VIT-04, and CL-08.

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Table 59. Incidence of Serious Adverse Events Stratified by Total Dose of FCM (Oral Iron Controlled Studies) (Continued)

Population Preferred Term	Total Dose of FCM		
	0-1000 mg (N=166)	1001-1400 mg (N=429)	>1400 mg (N=462)
Colon cancer	1 (0.6%)	0	0
Ovarian cancer	1 (0.6%)	0	0
Rectal cancer	0	1 (0.2%)	0
Peripartum cardiomyopathy	1 (0.6%)	0	0
Metrorrhagia	0	1 (0.2%)	0
Uterine haemorrhage	0	1 (0.2%)	1 (0.2%)
Pulmonary embolism	0	0	1 (0.2%)
Pulmonary oedema	0	0	1 (0.2%)
Vaginal hysterectomy	0	1 (0.2%)	0
Poor venous access	0	1 (0.2%)	0

Includes Studies VIT-11, VIT-01, VIT-09, VIT-02/VIT-03, VIT-04, and CL-08.

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Table 60. Incidence of Serious Adverse Events Stratified by Total Dose of FCM (HD Subjects)

Population Preferred Term	Total Dose of FCM		
	0-1000 mg (N=56)	1001-1400 mg (N=167)	>1400 mg (N=77)
≥1 Serious Adverse Event	9 (16.1%)	7 (4.2%)	3 (3.9%)
Cardio-respiratory arrest	1 (1.8%)	0	0
Myocardial infarction	1 (1.8%)	1 (0.6%)	0
Diarrhoea	1 (1.8%)	0	0
Haematemesis	0	1 (0.6%)	0
Nausea	0	1 (0.6%)	0
Pancreatitis	0	1 (0.6%)	0
Vomiting	0	1 (0.6%)	0
Catheter related complication	0	1 (0.6%)	0
Catheter site haemorrhage	0	1 (0.6%)	0
Pyrexia	0	1 (0.6%)	0
Rigors	0	1 (0.6%)	0
Bacterial sepsis	1 (1.8%)	0	0
Bronchpneumonia	1 (1.8%)	0	0
Pneumonia	0	0	1 (1.3%)
Pulmonary tuberculosis	0	1 (0.6%)	0
Respiratory tract infection	1 (1.8%)	0	0
Arteriovenous fistula thrombosis	0	0	1 (1.3%)
Fall	1 (1.8%)	0	0
Delirium	1 (1.8%)	0	0
Pulmonary oedema	1 (1.8%)	0	0
Arteriovenous fistula operation	0	0	1 (1.3%)
Renal transplant	1 (1.8%)	2 (1.2%)	1 (1.3%)
Haematoma	0	1 (0.6%)	0
Hypertension	1 (1.8%)	0	0
Shock	0	1 (0.6%)	0

Includes Studies VIT-015, VIT-53214 and hemodialysis subjects in VIT-06.

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No clear pattern of dose-response was observed for the incidence of adverse events or serious adverse events stratified by dose of FCM in the oral iron controlled studies (**Table 61**).

The incidence of treatment-emergent serious adverse events stratified by dose of FCM in HD Studies CL-015 and VIT-53214 and the HD subjects from Study VIT-06 is summarized in **Table 62**. Excluding the <400 mg group that had only 2 subjects, the highest incidence of treatment-emergent serious adverse events was observed in the 400 mg to 599 mg group following the first week of dosing (3.4% of subjects) and in the 600 mg to 799 mg group following the second week of dosing (1.9% of subjects).

The incidence of treatment-emergent serious adverse events stratified by dose of FCM in non-dialysis dependent chronic kidney disease Study VIT-04 is summarized in **Table 63**. No dose-related trends were observed.

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Table 61. Incidence of Serious Adverse Events in Stratified by Dose of FCM (Oral Iron Controlled Studies)

Population Preferred Term	Dose	Dose of FCM				
		<400 mg	400-599 mg	600-799 mg	800-999 mg	1000 mg
	First	N=9	N=7	N=121	N=353	N=567
≥1 Serious Adverse Event[1]		0	1 (14.3%)	0	4 (1.1%)	4 (0.7%)
Cardiac arrest		0	0	0	0	1 (0.2%)
Cardiac failure congestive		0	0	0	0	1 (0.2%)
Mitral valve prolapse		0	1 (14.3%)	0	0	0
Haemorrhoids		0	0	0	1 (0.3%)	0
Pyrexia		0	0	0	1 (0.3%)	0
Cholecystitis acute		0	0	0	0	1 (0.2%)
Endometritis decidual		0	0	0	1 (0.3%)	0
Pelvic inflammatory disease		0	0	0	1 (0.3%)	0
Pyelonephritis		0	0	0	1 (0.3%)	0
Skin infection		0	0	0	0	1 (0.2%)
Upper respiratory tract infection		0	0	0	0	1 (0.2%)
Metrorrhagia		0	0	0	1 (0.3%)	0
Pulmonary oedema		0	1 (14.3%)	0	0	0
	Second[2]	N=119	N=393	N=224	N=94	N=89
≥1 Serious Adverse Event		0	4 (1.0%)	0	1 (1.1%)	2 (2.2%)
Small intestinal haemorrhage		0	0	0	1 (1.1%)	0
Chest pain		0	0	0	0	1 (1.1%)
Cholecystitis		0	1 (0.3%)	0	0	0
Cellulitis		0	1 (0.3%)	0	0	0
Postoperative infection		0	0	0	0	1 (1.1%)
Sepsis		0	1 (0.3%)	0	0	0
Postoperative fever		0	1 (0.3%)	0	0	0
Uterine hemorrhage		0	1 (0.3%)	0	0	0
Vaginal hysterectomy		0	1 (0.3%)	0	0	0

Includes Studies VIT-11, VIT-01, VIT-09, VIT-02/VIT-03, VIT-04, and CL-08.

1 Subject 247 died from peripartum cardiomyopathy 8 days following her first dose in Study VIT-01 and did not receive a second dose. Because this summary includes only events within 7 days following the dose, the event of peripartum cardiomyopathy is not included in this summary.

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Table 62. Incidence of Serious Adverse Events Stratified by Dose of FCM (Hemodialysis Studies CL-015, VIT-53214, and VIT-06)

Population Preferred Term	Dose	Dose of FCM				
		<400 mg	400-599 mg	600-799 mg	800-999 mg	1000 mg
Hemodialysis	First Week Cumulative Dose	N=2	N=58	N=222	N=4	N=14
≥1 Serious Adverse Event		1 (50.0%)	2 (3.4%)	3 (1.4%)	0	0
Myocardial infarction		1 (50.0%)	0	0	0	0
Diarrhea		0	1 (1.7%)	0	0	0
Nausea		0	0	1 (0.5%)	0	0
Pyrexia		0	0	1 (0.5%)	0	0
Rigors		0	0	1 (0.5%)	0	0
Bacterial sepsis		0	0	1 (0.5%)	0	0
Bronchopneumonia		0	1 (1.7%)	0	0	0
Respiratory tract infection		0	1 (1.7%)	0	0	0
Renal transplant		0	0	1 (0.5%)	0	0
Hypertension		0	1 (1.7%)	0	0	0
	Second Week[1] Cumulative Dose	N=8	N=106	N=159	N=2	N=0
≥1 Serious Adverse Event		1 (12.5%)	0	3 (1.9%)	0	0
Hematemesis		0	0	1 (0.6%)	0	0
Vomiting		0	0	1 (0.6%)	0	0
Bronchopneumonia		1 (12.5%)	0	0	0	0
Pulmonary tuberculosis		0	0	1 (0.6%)	0	0
Renal transplant		0	0	1 (0.6%)	0	0

1 Does not include single dose crossover safety Study VIT-06.

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Table 63. Incidence of Serious Adverse Events Stratified by Dose of FCM (NDD-CKD Study VIT-04)

Population Preferred Term	Dosing Day	Low Dose Sample Size	High Dose Sample Size
Non-dialysis Dependent Chronic Kidney	**Day 0**	**< 1000 mg (N=35)**	**1000 mg (N=112)**
≥1 Serious Adverse Event		1 (2.9%)	2 (1.8%)
Cardiac failure congestive		0	1 (0.9%)
Myocardial infarction		1 (2.9%)	0
Skin infection		0	1 (0.9%)
Upper respiratory tract infection		0	1 (0.9%)
	Day 17	**No Dose (N=114)**	**500 mg (N=32)**
≥1 Serious Adverse Event		1 (0.9%)	1 (3.1%)
Pancreatitis acute		1 (0.9%)	0
Postoperative fever		0	1 (3.1%)
	Day 31	**No Dose (N=98)**	**500 mg (N=41)**
≥1 Serious Adverse Event		4 (4.1%)	1 (2.4%)
Cardiac failure congestive		1 (1.0%)	0
Cellulitis		0	1 (2.4%)
Sepsis		1 (1.0%)	0
Colon cancer		1 (1.0%)	0
Ovarian cancer		1 (1.0%)	0

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2.6.5.2 Maximum Hemoglobin Concentration

In the oral iron controlled studies, the highest incidence of serious adverse events by maximum hemoglobin achieved was observed in FCM and oral iron subjects whose maximum hemoglobin was <11 g/dL (**Table 64**). No clinically meaningful differences were observed between the groups for the overall proportion of subjects with any specific serious adverse events.

Table 64. Serious Adverse Events Experienced by ≥2 Subjects by Preferred Term, Treatment Group, and Maximum Hemoglobin (Oral Iron Controlled Studies)

	FCM			Oral Iron		
Preferred Term	**<11 g/dL (N=75)**	**11-14 g/dL (N=821)**	**>14 g/dL (N=138)**	**<11 g/dL (N=127)**	**11-14 g/dL (N=624)**	**>14 g/dL (N=62)**
At Least 1 Adverse Event	9 (12.0%)	20 (2.4%)	1 (0.7%)	9 (7.1%)	11 (1.8%)	0
Cardiac failure congestive	0	2 (0.2%)	0	1 (0.8%)	1 (0.2%)	0
Coronary artery disease	0	2 (0.2%)	0	0	0	0
Gastrointestinal haemorrhage	0	1 (0.1%)	0	2 (1.6%)	0	0
Sepsis	2 (2.7%)	0	0	0	0	0
Uterine haemorrhage	2 (2.7%)	0	0	0	1 (0.2%)	0

Includes Studies VIT-11, VIT-01, VIT-09, VIT-02/VIT-03, VIT-04, and CL-08.
Note: Table excludes 4 FCM subjects and 1 oral iron subject who experienced serious adverse events as they had no post-baseline hemoglobin values. These serious adverse events included peripartum cardiomyopathy, myocardial infarction, pulmonary edema, and cardiac arrest in the FCM group and renal failure chronic in the oral iron group.

2.6.6 Other Adverse Events of Special Interest

Known risks associated with administration of other intravenous iron products including hypotension, allergic and bioactive iron reactions have been evaluated for FCM administration in the sections that follow. Additionally, infections and cardiovascular events, each of which were underlying causes associated with death in more than 1 FCM subject, were evaluated.

2.6.6.1 Hypotension

No cases of symptomatic hypotension or severe or serious hypotension have been reported following FCM treatment.

Postpartum/HUB Studies

Of the 1052 postpartum and HUB FCM-treated subjects, 3 (0.3%) experienced adverse events of hypotension. Each of the events occurred in postpartum subjects, were considered study drug related by the Investigator, and were not symptomatic based on adverse event reports. All 3 events were considered mild in severity. The lowest systolic/diastolic blood pressure noted among the values that met the criteria was a decrease from 92/64 mmHg to 66/40 mmHg.

Oral Iron Controlled, Iron Sucrose Controlled, and Crossover Safety Studies

Of the 1057 subjects treated with FCM in the oral iron controlled studies, 8 (0.8%) experienced adverse events of hypotension. None of the subjects treated with oral iron experienced adverse events of hypotension. None of the hypotensive events was considered severe or serious, and none led to premature discontinuation of study drug. A total of 3 events (in the postpartum/HUB studies) discussed in the paragraph above were considered study drug related by the Investigator.

In the iron sucrose controlled studies, the incidence of hypotension was similar between the FCM and iron sucrose treatment groups, but higher than that observed in the oral iron controlled studies. As all of the events of hypotension reported in the iron sucrose controlled studies were from Study CL-15, the observed difference in incidence of hypotension between the oral iron controlled and iron sucrose controlled studies is likely due to the different study population treated (primarily the hemodialysis population). The incidence of hypotension considered related to treatment was notably higher in the iron sucrose group (3.4%) than the FCM group (0.7%). One event in the FCM group was considered study drug related by the Investigator.

In the crossover safety trial, which was specifically designed to evaluate the acute safety and tolerability of a 15 mg/kg dose (maximum of 1000 mg) of FCM compared to placebo, no subjects reported hypotension after receiving FCM compared to 1 report after receipt of placebo.

The incidence of adverse events of hypotension in the oral iron controlled, iron sucrose controlled, and crossover safety studies is presented in **Table 65**.

Table 65. Adverse Events of Hypotension by Treatment Group (Oral Iron Controlled, Iron Sucrose Controlled, and Crossover Safety Studies)

	Oral Iron Controlled		Iron Sucrose Controlled		Crossover Safety Study	
Preferred Term	**FCM (N=1057)**	**Oral Iron (N=834)**	**FCM (N=149)**	**Iron Sucrose (N=145)**	**FCM (N=584)**	**Placebo (N=569)**
All Adverse Events						
Hypotension	8 (0.8%)	0	12 (8.1%)	12 (8.3%)	0	1 (0.2%)
Procedural Hypotension	0	0	2 (1.3%)	1 (0.7%)	0	0
Related Adverse Events						
Hypotension	3 (0.3%)	0	1 (0.7%)	5 (3.4%)	0	0

Includes: Oral Iron Controlled Studies VIT-11, VIT-01, VIT-09, VIT-02/VIT-03, VIT-04, and CL-08; Iron Sucrose Controlled Studies CL-15 and CARS; and Crossover Safety Study VIT-06.

All Multicenter Studies Excluding the Extension Study

Of the 29 FCM subjects with adverse events of hypotension across all multicenter studies excluding the extension study, only 5 subjects had events considered drug-related by the investigator (4 previously discussed events and 1 additional event in Study VIT-53214). All of the related hypotensive events were considered mild to moderate in intensity, with most being mild, and none led to premature discontinuation of study drug. Additionally, all of the episodes of related hypotension were not symptomatic based on adverse event reports. The hypotensive events in 2 of the 5 subjects, both from studies of HD, occurred during the HD procedure and required treatment with fluids.

Extension Study

Three subjects in the long-term extension study (VIT-05) experienced hypotensive events. Of these subjects, 1 experienced a hypotensive event that was considered possibly related to FCM by the Investigator. The hypotensive event, which was considered moderate in severity, occurred 103 days after the last dose of FCM and was asymptomatic. The event was noted to have resolved after discontinuation of hydrochlorothiazide.

2.6.6.2 Allergic Reactions

Preclinical and clinical safety data support the fact that serious hypersensitivity reactions are not associated with FCM. Guinea pigs immunized with dextran antibodies did not react to FCM indicating that the test compound does not cross react with dextran antibodies. No serious hypersensitivity reactions have been reported in FCM-treated subjects.

Oral Iron Controlled Studies

Adverse events indicative of potential allergic reactions in the oral iron controlled studies are presented by treatment group in **Table 66**. Each of these events was reported by <2% of subjects who were treated with FCM, except for rash, which was reported by 2.1% of subjects. The urticaria-related events following FCM dosing were generally mild in severity and resolved within 2 hours. The onset of rashes that were described as flushing or maculopapular occurred during or immediately after FCM administration, and resolved between minutes and 3 hours after FCM administration.

Table 66. Adverse Events Indicative of Potential Allergic Reactions by Treatment Group (Oral Iron Controlled Studies)

SOC Preferred Term	FCM (N=1057)	Oral Iron (N=834)
At Least 1 Adverse Event	49 (4.6%)	16 (1.9%)
Bronchospasm	0	1 (0.1%)
Eye pruritus	1 (0.1%)	0
Genital pruritus female	1 (0.1%)	0
Idiopathic urticaria	1 (0.1%)	0
Infusion site pruritus	1 (0.1%)	0
Pruritus	9 (0.9%)	2 (0.2%)
Pruritus generalized	0	1 (0.1%)
Pruritus genital	1 (0.1%)	0
Rash	22 (2.1%)	10 (1.2%)
Rash erythematous	3 (0.3%)	0
Rash macular	3 (0.3%)	0
Rash maculopapular	1 (0.1%)	0
Rash pruritic	2 (0.2%)	1 (0.1%)
Urticaria	9 (0.9%)	3 (0.4%)
Urticaria generalized	1 (0.1%)	0
Wheezing	1 (0.1%)	0

Includes Studies VIT-11, VIT-01, VIT-09, VIT-02/VIT-03, VIT-04, and CL-08.

All Multicenter Studies Excluding Extension Study

Adverse events indicative of potential allergic reactions in all multicenter studies excluding the extension study are presented by treatment group in **Table 67**. Each of these events, including rash, pruritus, and urticaria, was reported by <2% of subjects who were treated with FCM. None of these events was serious and few led to discontinuation of study drug (rash: 4 subjects, urticaria 2 subjects, pruritus and rash erythematous: 1 subject each).

Table 67. Adverse Events Indicative of Potential Allergic Reactions by Treatment Group (All Multicenter Studies Excluding Extension Study)

SOC Preferred Term	FCM (N=1414)	Oral Iron (N=834)	Venofer (N=145)	Placebo (N=15)	Crossover Safety Study FCM (N=584)	Crossover Safety Study 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 popular	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

Includes Studies VIT-11, VIT-01, VIT-09, VIT-02/VIT-03, CL-03, CL-08, VIT-04, CL-15, VIT-53214, VIT-06, and CARS.

The verbatim descriptions of rash and urticaria events were reviewed in order to characterize events that might represent allergic reactions. When events such as incisional rash from surgery and rashes starting weeks or months after dosing were excluded, there were 13 FCM-treated subjects who had urticaria-related events and 30 FCM-treated subjects who had non-urticaria related events that might represent allergic reactions.

The urticaria-related events following FCM dosing were generally mild in severity and resolved within 2 hours. Seven of the 13 subjects received another FCM dose and none of the 7 subjects had a rash recurrence.

Thirty subjects had non-urticaria related rashes that were described as flushing or maculopapular. Onset of these rashes occurred during or immediately after FCM administration, and resolved between minutes and 3 hours after FCM administration. Nine of the 30 subjects received another FCM dose and 3 of the 9 subjects had a pruritic rash that resolved between 50 minutes and 3.5 hours after FCM administration.

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Of the 1998 subjects treated with FCM in the multicenter studies and the placebo-controlled, single-dose crossover safety study, only 3 (0.2%) experienced adverse events that were reported as hypersensitivity (**Table 68**). One oral iron subject experienced an adverse event of hypersensitivity.

Table 68. Adverse Events of Hypersensivity by Treatment Group (All Multicenter Studies Excluding Extension Study)

SOC Preferred Term					Crossover Safety Study	
	FCM (N=1414)	Oral Iron (N=834)	Venofer (N=145)	Placebo (N=15)	FCM (N=584)	Placebo (N=569)
All Hypersensivity Events	3 (0.2%)	1 (0.1%)	0	0	0	0

Includes Studies VIT-11, VIT-01, VIT-09, VIT-02/VIT-03, CL-03, CL-08, VIT-04, CL-15, VIT-53214, VIT-06, and CARS.

Of the 3 treatment-emergent adverse events of hypersensitivity experienced in FCM subjects, 1 was reported in Study CL-08, 1 was reported in Study VIT-09, and 1 was reported in Study CARS. The 3 events were poorly described; however, they were not associated with vital sign changes (e.g., hypotension and tachycardia), treatment with epinephrine was not required, and admittance to an emergency room or hospital was not necessary. After their event had resolved, 1 subject was re-dosed without incident.

The hypersensitivity event reported in Study CL-08 was mild in intensity and considered possibly related to study medication. The event occurred on the same day as the first dose of study medication administration.

The hypersensitivity event reported in Study VIT-09 was by a subject who had no relevant medical history and received infusions of 800 mg of FCM at Baseline and 9 days later. 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 severe and certainly related to study drug by the investigator and resolved without sequelae within 5 days.

The hypersensitivity event reported in Study CARS 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 FCM). 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.

2.6.6.3 Bioactive Iron Reactions

Serious reactions associated with bioactive iron, such as symptomatic hypotension and syncope have not been seen with FCM.

Bioactive iron reactions may be seen toward the end of treatment or immediately after treatment, most commonly when intravenous iron agents are administered at doses or infusion rates that exceed recommendations. They are characterized by hypotension without allergic signs or symptoms, with pain in the flank, abdomen or chest with nausea, vomiting, or diarrhea. One placebo-controlled, blinded crossover safety study (Study VIT-06) specified contact with subjects within 24 hours after treatment to assess any adverse experiences immediately following treatment. No adverse events consistent with bioactive iron reactions were observed in Study VIT-06. None of the subjects experienced hypotension following FCM administration. A slightly higher rate of nausea (3.0%) was observed after dosing with FCM compared with placebo

(1.4%); however, the incidence of other adverse events that occurred within 24 hours of dosing were generally comparable after dosing with either FCM or placebo. All of the adverse events that occurred within 24 hours of dosing were mild or moderate in severity, except for 2 events of blood phosphorus decreased following placebo dosing (both subjects had received FCM during the first treatment period and placebo in the second treatment period) and 1 event of headache following FCM dosing that were considered severe. A summary of adverse events indicative of potential bioactive iron reactions that occurred within 24 hours of treatment and were reported in more than 1 subject in Study VIT-06 is presented in **Table 69**.

Table 69. Adverse Events Indicative of Potential Bioactive Iron Reactions Reported by >1 Subject Within 24 Hours of Treatment (Completer Population; Crossover Safety Study VIT-06)

Preferred Term	FCM (N=559)	Placebo (N=559)
At Least 1 Adverse Event	84 (15.0%)	64 (11.4%)
Nausea	17 (3.0%)	8 (1.4%)
Dizziness	7 (1.3%)	3 (0.5%)
Dyspepsia	4 (0.7%)	0
Diarrhoea	3 (0.5%)	6 (1.1%)
Abdominal pain	3 (0.5%)	1 (0.2%)
Vomiting	2 (0.4%)	1 (0.2%)
Chest pain	2 (0.4%)	1 (0.2%)
Back pain	2 (0.4%)	2 (0.4%)
Dyspnoea	2 (0.4%)	0
Abdominal discomfort	0	2 (0.4%)

Completer Population includes subjects who completed both the FCM and placebo dosing periods.

All Adverse Events in Crossover Safety Study VIT-06

During the 7-day Treatment Period in the Completer Population, at least 1 adverse event was experienced by 29.3% (164/559) of the subjects after receiving FCM and 19.7% (110/559) of the subjects after receiving placebo. Adverse events experienced by ≥3% of subjects after receiving FCM were headache (5.4%) and nausea (3.8%). The only adverse event experienced by ≥3% of subjects after receiving placebo was headache (3.4%). A summary of adverse events experienced by ≥1% subjects in either treatment during the 7-day Treatment Period in the Completer Population is presented in **Table 70**.

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Table 70. Adverse Events Experienced by ≥1% Subjects in Either Treatment During the 7-Day Treatment Period (Completer Population; Crossover Safety Study VIT-06)

MedDRA SOC Preferred Term	FCM (N=559)	Placebo (N=559)
At Least 1 Adverse Event	**164 (29.3%)**	**110 (19.7%)**
Gastrointestinal Disorders	46 (8.2%)	32 (5.7%)
Diarrhoea	7 (1.3%)	9 (1.6%)
Nausea	21 (3.8%)	10 (1.8%)
General Disorders and Administration Site Conditions	32 (5.7%)	11 (2.0%)
Pyrexia	7 (1.3%)	1 (0.2%)
Fatigue	7 (1.3%)	0 (0.0%)
Investigations	17 (3.0%)	10 (1.8%)
Alanine Aminotransferase Increased	9 (1.6%)	2 (0.4%)
Aspartate Aminotransferase Increased	9 (1.6%)	1 (0.2%)
Nervous System Disorders	45 (8.1%)	30 (5.4%)
Headache	30 (5.4%)	19 (3.4%)
Dizziness	10 (1.8%)	3 (0.5%)
Skin and Subcutaneous Tissue Disorders	15 (2.7%)	10 (1.8%)
Rash	6 (1.1%)	2 (0.4%)

Completer Population includes subjects who completed both the FCM and placebo dosing periods.

2.6.6.4 Infections

Postpartum and HUB Studies

The overall incidences of adverse events or serious adverse events associated with infections and infestations were similar between postpartum and HUB subjects treated with either FCM (14.0% and 0.8%, respectively) or oral iron (13.5% and 0.4%, respectively) (**Table 71** and **Table 72**, respectively). None of the serious adverse events associated with infections and infestations experienced by postpartum and HUB subjects were considered by the investigator to be related to treatment. Additionally, the overall incidence of adverse events associated with infections and infestations were similar between postpartum and HUB subjects treated in the crossover safety study after receiving either FCM (2.9%) or placebo (3.4%). None of the subjects in the crossover safety study experienced a serious adverse event associated with infections or infestations.

Table 71. Adverse Events Associated with Infections and Infestations (≥1.0% in Either Group) by System Organ Class, Preferred Term, and Treatment Group (All Postpartum and HUB Study Subects)

	Oral Iron Controlled Studies[a]		Placebo-Controlled, Single-Dose, Crossover Safety Study[b]	
SOC Preferred Term	**FCM (N=773)**	**Oral Iron (N=668)**	**FCM (N=279)**	**Placebo (N=263)**
Infections and Infestations	108 (14.0%)	90 (13.5%)	9 (3.2%)	11 (4.2%)
Nasopharyngitis	18 (2.3%)	21 (3.1%)	3 (1.1%)	2 (0.8%)
Upper Respiratory Tract Infection	11 (1.4%)	9 (1.3%)	0	1 (0.4%)
Sinusitis	10 (1.3%)	8 (1.2%)	1 (0.4%)	0
Urinary Tract Infection	9 (1.2%)	12 (1.8%)	0	3 (1.1%)
Influenza	8 (1.0%)	5 (0.7%)	0	2 (0.8%)

a Includes Studies VIT-11, VIT-01, VIT-09, and VIT-02/VIT-03
b Includes Study VIT-06

Table 72. All Serious Adverse Events Associated with Infections and Infestations by System Organ Class, Preferred Term, and Treatment Group (All Postpartum and HUB Study Subects)

SOC Preferred Term	Oral Iron Controlled Studies[a]		Placebo-Controlled, Single-Dose, Crossover Safety Study[b]	
	FCM (N=773)	Oral Iron (N=668)	FCM (N=279)	Placebo (N=263)
Infections and Infestations	6 (0.8%)	3 (0.4%)	0	0
Appendicitis	1 (0.1%)	0	0	0
Endometritis Decidual	1 (0.1%)	0	0	0
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	1 (0.1%)	0	0	0
Endometritis	0	2 (0.3%)	0	0
Pelvic Abscess	0	2 (0.3%)	0	0

a Includes Studies VIT-11, VIT-01, VIT-09, and VIT-02/VIT-03
b Includes Study VIT-06

Oral Iron Controlled Studies

The overall incidences of adverse events or serious adverse events associated with infections and infestations were similar between subjects treated with either FCM (13.6% and 0.9% respectively) or oral iron (12.4% and 0.4%, respectively) in the oral iron controlled studies (**Table 73** and **Table 74**, respectively). None of the serious adverse events experienced in the oral iron controlled studies were considered by the Investigator to be related to treatment.

Table 73. Adverse Events Associated with Infections and Infestations (≥2.0% in Either Group) by System Organ Class, Preferred Term, and Treatment Group (Oral Iron Controlled Studies)

SOC Preferred Term	FCM (N=1057)	Oral Iron (N=834)	p-value
Infections and infestations	144 (13.6%)	103 (12.4%)	0.4498
Nasopharyngitis	22 (2.1%)	24 (2.9%)	

Includes Studies VIT-11, VIT-01, VIT-09, VIT-02/VIT-03, VIT-04, and CL-08.

Table 74. Serious Adverse Events Associated with Infections and Infestations Experienced by ≥ 2 Subjects in Any Group by System Organ Class, Preferred Term, and Treatment Group (Oral Iron Controlled Studies)

SOC Preferred Term	FCM (N=1057)	Oral Iron (N=834)
Infections and infestations	10 (0.9%)	3 (0.4%)
Endometritis	0	2 (0.2%)
Pelvic abscess	0	2 (0.2%)
Sepsis	2 (0.2%)	0

Includes Studies VIT-11, VIT-01, VIT-09, VIT-02/VIT-03, VIT-04, and CL-08.

Iron Sucrose Controlled Studies

The overall incidences of adverse events or serious adverse events associated with infections and infestations were similar between subjects treated with either FCM (8.7% and 0.7% respectively) or iron sucrose (8.3% and 1.4%, respectively) in the iron sucrose controlled studies (**Table 75** and **Table 76**, respectively). None of the serious adverse events experienced in the iron sucrose controlled studies were considered by the Investigator to be related to treatment.

Table 75. Adverse Events Associated with Infections or Infestations (≥ 2.0% in Any Group) by System Organ Class, Preferred Term, and Treatment Group (Iron Sucrose Controlled Studies)

SOC Preferred Term	FCM (N=149)	Iron Sucrose (N=145)
Infections and infestations	13 (8.7%)	12 (8.3%)
Nasopharyngitis	3 (2.0%)	0

Includes Studies CL-15 and CARS.

Table 76. Serious Adverse Events Associated with Infections or Infestations by System Organ Class, Preferred Term, and Treatment Group (All Iron Sucrose Controlled Studies)

SOC Preferred Term	FCM (N=149)	Iron Sucrose (N=145)
Infections and infestations	1 (0.7%)	2 (1.4%)
Bacterial sepsis	1 (0.7%)	0
Genitourinary tract Infection	0	1 (0.7%)
Lung infection	0	1 (0.7%)
Pseudomonal sepsis	0	1 (0.7%)

Includes Studies CL-15 and CARS.

2.6.6.5 Serious Cardiac and Ischemic Cardiovascular Events

2.6.6.5.1 Serious Cardiac Events

Postpartum/HUB Studies

In the postpartum and HUB controlled studies, the incidence of serious cardiovascular adverse events was similar between the FCM and oral iron groups (**Table 77**). Two subjects in the FCM group (0.3%) and 1 subject in the oral iron group (0.1%) experienced at least 1 serious cardiovascular adverse event. None of these events were considered by the Investigator to be related to study drug.

Table 77. Serious Cardiovascular Adverse Events by Preferred Term and Treatment Group (Postpartum and HUB Controlled Studies)

Preferred Term	FCM (N=773)	Oral Iron (N=668)
At Least 1 Adverse Event	2 (0.3%)	1 (0.1%)
Cardiac Failure	1 (0.1%) [VIT-01]	0
Cardiac Failure Congestive	0	1 (0.1%) [VIT-01]
Mitral Valve Prolapse	1 (0.1%) [VIT-11]	0

Includes Studies VIT-11, VIT-01, VIT-09, VIT-02/VIT-03.
[Identifies the study in which the event occurred.]

Oral Iron Controlled Studies Excluding Postpartum and HUB Studies

In the oral iron controlled studies excluding the postpartum and HUB studies, the incidence of serious cardiovascular adverse events was 2.5% in the FCM group and 1.2% in the oral iron group (**Table 78**). All of the serious cardiac events were from subjects with an underlying disease of NDD-CKD, with the exception of 1 event of cardiac arrest and 1 event of tachycardia which were from IBD subjects. The event of Tachycardia was due to anemia secondary to IBD that occurred 21 days after the subject's last dose of FCM and resolved without treatment. The event of palpitations occurred 47 days after the last dose of FCM in a paced patient, no treatment was required. None of these events were considered by the Investigator to be related to study drug.

Table 78. Serious Cardiovascular Adverse Events by Preferred Term and Treatment Group (Oral Iron Controlled Studies Excluding Postpartum and HUB Controlled Studies)

Preferred Term	FCM (N=284)	Oral Iron (N=166)
At Least 1 Adverse Event	7 (2.5%)	2 (1.2%)
Cardiac Arrest	1 (0.3%) [IBD]	0
Cardiac Failure Congestive	2 (0.7%) [NDD-CKD]	1 (0.6%) [NDD-CKD]
Coronary Artery Disease	2 (0.7%) [NDD-CKD]	0
Myocardial Infarction	1 (0.3%) [NDD-CKD]	0
Myocardial Ischemia	0	1 (0.6%) [NDD-CKD]
Palpitations	1 (0.3%) [NDD-CKD]	0
Tachycardia	1 (0.3%) [IBD]	0

Includes Studies VIT-04, and CL-08.
[Identifies the population in which the event occurred.]

2.6.6.5.2 Serious Cardiovascular Ischemic Events

The Luitpold medical monitor performed a blinded review of preferred terms and selected those terms that have been noted in the literature as confirmed cardiovascular ischemic adverse events. After identification of the appropriate terms, summary tables were constructed for the oral iron controlled studies and the iron sucrose controlled studies and results are presented below.

Oral Iron Controlled Studies

In the oral iron controlled studies, the incidence of confirmed serious cardiovascular ischemic adverse events was similar between the FCM and oral iron groups (**Table 79**). A total of 3 subjects in both the FCM (0.3%) and oral iron (0.4%) groups experienced at least 1 confirmed serious cardiovascular ischemic adverse event. None of these events were considered by the Investigator to be related to study drug.

Table 79. Confirmed Serious Cardiovascular Ischemic Adverse Events by Preferred Term and Treatment Group (Oral Iron Controlled Studies)

Preferred Term	FCM (N=1057)	Oral Iron (N=834)
At Least 1 Adverse Event	3 (0.3%)	3 (0.4%)
Myocardial infarction	1 (0.1%)	0
Coronary artery disease	2 (0.2%)	0
Myocardial ischaemia	0	1 (0.1%)
Cerebrovascular accident	0	1 (0.1%)
Transient ischaemic attack	0	1 (0.1%)

Includes Studies VIT-11, VIT-01, VIT-09, VIT-02/VIT-03, VIT-04, and CL-08.

Iron Sucrose Controlled Studies

In the iron sucrose controlled studies, the incidence of confirmed serious cardiovascular ischemic adverse events was 2.0% in the FCM group and 0.7% in the iron sucrose group (**Table 80**). In the FCM group, 2 subjects reported myocardial infarction and 1 reported unstable angina. In the iron sucrose group, 1 subject reported myocardial infarction. None of these events were considered by the Investigator to be related to study drug.

Table 80. Confirmed Serious Cardiovascular Ischemic Adverse Events by Preferred Term and Treatment Group (Iron Sucrose Controlled Studies)

Preferred Term	FCM (N=149)	Iron Sucrose (N=145)
At Least 1 Adverse Event	3 (2.0%)	1 (0.7%)
Myocardial infarction	2 (1.3%)	1 (0.7%)
Unstable angina	1 (0.7%)	0

Includes Studies CL-15 and CARS.

2.6.7 Deaths

Eleven deaths were reported in the entire FCM development program. All eleven deaths were judged to be unrelated to study drug by Investigators.

Five deaths were reported following treatment with FCM and 1 death following treatment with iron sucrose in parallel-group controlled trials. In these postpartum and heavy uterine bleeding (HUB) studies, 1 postpartum subject died from autopsy-proven peripartum cardiomyopathy. Of the 4 remaining deaths following FCM, 3 were subjects with chronic kidney disease (CKD) and 1 was a subject with inflammatory bowel disease (IBD).

Five deaths were reported in uncontrolled studies: 4 subjects with CKD and 1 subject with iron deficiency anemia (IDA). The etiology of all the deaths was variable and no clinically important pattern was observed. All 11 deaths were judged to be unrelated to study drug.

An independent, external group of experts with expertise in iron therapeutics, clinical pharmacology, epidemiology, nephrology, cardiology and pathology was convened to assess the possible role of FCM treatment in the deaths. The group considered the possible relationship of dose, time between dose and event, phosphate levels, and reported cause of death. In addition,

analytical challenges in comparing treatment groups across disparate populations were addressed by experts in statistics and epidemiology.

2.6.7.1 Comparability of Risk

Unbiased comparison of treatment groups for deaths must account for treatment group differences in numbers of subjects and length of observation, as well as treatment group differences in the baseline (intrinsic) mortality risk. There were over twice as many subjects exposed to FCM as in the control groups and the length of observation for FCM was over twice that of oral iron (**Table 81**). This difference arises from 2:1 randomization schedules and uncontrolled studies of FCM. Therefore, treatment group comparisons must focus on incidence rates and mortality rates per 100 patient years.

Table 81. Exposure in FCM Studies

	FCM		Control	
Population	**Number of Subjects**	**Patient Years of Follow-up**	**Number of Subjects**	**Patient Years of Follow-up**
Controlled Studies				
Postpartum/HUB	773	115.1	668	90.0
Hemodialysis	119	15.4	118	14.7
Nondialysis CKD	147	22.8	103	14.7
IBD	137	30.7	63	12.9
Chronic Heart Failure	30	6.4	42	8.5
Phase 1	24	0.5	8	0.2
Subtotal	1230	190.9	1002	141.0
Uncontrolled Studies				
	925[a]	119.1	0	0
Total	2080[a]	310.0	1002	141.0

HUB = heavy uterine bleeding, CKD = chronic kidney disease, IBD = inflammatory bowel disease
a There were 75 subjects who received FCM in both a controlled study and an uncontrolled extension study. Thus, there were 2080 unique exposures.

As seen in **Table 82**, the intrinsic risk of death varies substantially across the patient populations included in the development program. Mortality rates based on all combined studies are biased because the uncontrolled studies were conducted primarily in the high risk populations. Comparisons based on randomized controlled studies decrease this bias because the concurrent control provides an estimate of the intrinsic mortality risk in the population. However, the interpretation of mortality rates combined across disparate populations is uncertain. Treatment group comparisons are thus best made in combinations of randomized controlled studies with populations of similar intrinsic mortality risk.

Table 82. Baseline Mortality Risk and Mortality Risk Per 100 patient Years for Specific Causes of Death in Specified Population Groups in the US

Specified Population Groups	Mortality Risk	Mortality Risk per 100 Patient Years
HD[a]	18.6%	18.6
NDD-CKD[b]	7.5%	7.5
IBD[c]	0.2%	0.2
Postpartum[d]	<0.0025%	0.0025
HUB	NR	NR

NR = not reported for mortality rate << 0.1 per 100,000 population in specified group.
Sources: Data derived and calculated from:
a: US Renal Data System (US Renal Data System 2006 Annual Report [www.usrds.org/adr.htm]).
b: AJKD 2005:46[5]
c: NIH (Everhart JE. Digestive diseases in the US: Epidemiology and Impact – National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of National Institute of Health (NIH) Publication No. 94-1447, 1994.)
d: CDC

In order to reduce the bias for treatment group comparisons, the primary population for mortality comparisons is the combined postpartum and HUB studies. These studies are in the targeted population, have low intrinsic baseline mortality risk, and have similar exposure/follow-up for the 2 treatment groups. The combination of all other parallel-group, randomized studies provides a supportive population for mortality comparisons. This population includes subjects with higher baseline mortality risk such as chronic kidney disease (non-dialysis dependent and hemodialysis dependent), IBD, and heart failure. Patient-years of follow-up is also larger in the FCM group (75.8 years) as compared to the control group (51.1 years; **Table 83**). Finally, descriptive summary statistics are provided for the uncontrolled studies that include higher-risk subjects and lack a control group to estimate the intrinsic mortality risk for the study populations.

2.6.7.2 Observed Mortality Rate

A summary of the observed mortality rate is presented for each study population in **Table 83**. In general, the observed mortality rates are consistent with the baseline mortality risks in **Table 82**. Note that the patient-years of exposure for the population of uncontrolled studies are disproportionally influenced by subjects in Study VIT-05 who were followed up to 44 weeks. It is not clear whether the estimated mortality rate per 100 patient-years in this population could be biased as a result of combining this long follow-up with the shorter follow-up in the other uncontrolled studies

Table 83. Observed Mortality Rate in FCM Clinical Program in Parallel-Group Studies as of 31 August 2007

	Mortality Rate for FCM		Mortality Rate for Control Subjects[a,b]	
Population	Total	Deaths/100 Patient Years	Total	Deaths/100 Patient Years
Postpartum/HUB Controlled Studies	1/773 (0.13%)	0.87 (PY[c]=115.1)	0/668 (0)	0 (PY=90.0)
Other Controlled Studies	4/457 (0.88%)	5.28 (PY=75.8)	1/334 (0.30%)	1.96 (PY=51.1)
Uncontrolled Studies	5/925 (0.54%)	4.20 (PY=119.1)	NA	NA

[a] Subjects in crossover safety Study VIT-06 received FCM within ±7 days of the placebo dose and are included only in the uncontrolled study population.
[b] Control group includes iron sucrose, oral iron, and placebo

[c] PY=Patient years

2.6.7.3 Clinical Evidence for Possible Mechanisms

The potential predictive value of anaphylaxis, bioactive iron reactions, rate of hemoglobin rise, hemoglobin >13 g/dL, hypophosphatemia, baseline mortality risk and FCM dose on the mortality rate was explored.

No death was consistent with the expected timing of anaphylaxis or bioactive iron reactions in relation to FCM administration. No death was consistent with an allergic, anaphylactic, or bioactive iron reaction mechanism. No patient administered FCM demonstrated allergic reactions consistent with anaphylaxis. No patient administered FCM in clinical trials has demonstrated symptoms or findings consistent with bioactive iron reaction. The absence of bioactive iron reactions after rapid administration of high doses of FCM confirms in vitro information that iron in FCM is tightly bound and, in serum, is not dialyzable or available for donation to transferrin.

Rate of rise in hemoglobin during the study had no negative effect on the serious adverse event rate in FCM clinical trials. No patient receiving FCM was simultaneously initiated on epoetin therapy, the presumptive causal agent in adverse cardiovascular events related to rapid hemoglobin rise in patients with chronic kidney disease. Rapid hemoglobin rise was commonly seen after either FCM or oral iron treatment, but as expected, hypertension, hypertensive emergencies, and signs of fluid overload were not seen. One hypertensive hemodialysis subject had a rapid rise with hemoglobin reaching 10.1 g/dL, 8 days prior to death (see Appendix B, Section 5.2.1 for case discussion). No other death cases had a rapid rise in hemoglobin. Those deaths that occurred before follow-up hemoglobin could be obtained would have also occurred before hemoglobin could have risen significantly, if at all.

Serious adverse event rates were convincingly associated with lower rather than higher observed hemoglobin levels (**Table 64**), presumably reflecting the increased disease burden associated with severe anemia. Unlike ESA treatment, the administration of iron does not stimulate erythropoeiesis, but rather enables erythropoiesis to achieve normal hemoglobin levels. Thus, iron therapy in any form cannot generate hemoglobin levels above what is physiologically normal for the patient, and therefore cannot generate "excessive" hemoglobin levels. If the patient receives more iron than is needed to restore the hemoglobin to normal, the hemoglobin does not rise further. Rather, the excessive iron is stored for future use.

The deaths occurred in subjects for whom the observed phosphate values at the time of the serious adverse event leading to death were not significantly low, or in subjects whose death occurred too early after FCM administration for hypophosphatemia to have developed.

The mortality rate was related primarily to the baseline mortality risk (as shown in Table 82) of the clinical trial populations (**Table 84**). That is, the mortality rate was highest in the HD and NDD-CKD populations and lowest in the postpartum and HUB populations.

Table 84. Mortality by Baseline Mortality Risk in Parallel-Group Controlled Studies

Population	FCM Incidence	Control Incidence	Probability of No Control Deaths[a]	Fisher's Exact Test[b]
PP/HUB	1/773 (0.13%)	0/668	41.9%	>0.9999
HD	1/119 (0.84%)	0/118	37.0%	>0.9999
NDD-CKD	2/147 (1.36%)	0/103	24.4%	0.5135
IBD	1/137 (0.73%)	0/63	63.0%	>0.9999
CHF	0/30	1/42 (2.38%)	NA	>0.9999

PP = postpartum; HUB = heavy uterine bleeding; HD = hemodialysis; NDD = non-dialysis dependent chronic kidney disease; IBD = inflammatory bowel disease; CHF = congestive heart failure
a Given observed rate for FCM
b Comparing FCM vs control

Because the risk of infection in CKD patients is high we also investigated any association between infection and mortality. The overall incidences of adverse events or serious adverse events associated with infections were similar between FCM and controls. In the key patient population currently receiving high doses of intravenous iron, anemic patients with chronic kidney disease undergoing chronic hemodialysis, the evidence is conclusive that there is no link between intravenous iron administration and infection. Though hemodialysis patients are prone to infection and receive an average of 3.1 grams of intravenous iron annually,[63] prospective observational trials,[64] randomized controlled trials,[64] and retrospective analysis of large scale United States dialysis databases[65] have failed to demonstrate a relationship between intravenous iron administration and risk of infection.

Among subjects treated with FCM, the number of doses received ranged from 1 to 11; however, the majority of the subjects received ≤3 doses of FCM. The overall observed mortality rate did not appear related to number of doses, total dose, maximum single dose, or last single dose received prior to death as shown in **Table 85**.

Table 85. Crude Mortality Risk by Level of FCM Exposure as of 31 August 2007

FCM Exposure	Total Deaths	Total FCM Subjects	Crude Mortality Risk
Number of Doses			
1	5	723	**0.69%**
2-3	3	989	0.30%
4-5	1	88	1.14%
6-7	1	195	0.51%
8-9	0	74	0
10-11	0	11	0
Total Dose			
0 -1000 mg	6	812	**0.74%**
1001 to 1400 mg	1	619	0.16%
>1400 mg	3	649	0.46%
Maximum Single Dose			
<400 mg	3	331	**0.91%**
400-499 mg	0	1	0
500-599 mg	0	41	0
600-799 mg	0	158	0
800-999 mg	0	475	0
1000 mg	7	1074	0.65%
Last Single Dose			
<500 mg	3	718	0.42%
500 mg	3	302	**0.99%**
501-999 mg	0	514	0
1000 mg	4	546	0.73%

The highest observed mortality rate within each category is **bolded**.

2.6.7.4 Probabilistic Assessments

Given observed mortality rate for FCM, the probability of the observed number or fewer deaths for the control group is high as shown in **Table 86**. The probability of no deaths in the control group in postpartum/HUB is 41.9% and the probability of 1 or fewer deaths in the control group for other controlled studies is 20.7%.

Table 86. Probability of Observed or Fewer Number of Deaths in the Control Group in Each Population from Completed Studies When Observed Mortality Rate Equals That Observed for FCM

	Population-specific Mortality Rate			
Study Status Population	FCM Rate	Observed Control Deaths	Number of Control Subjects[1]	Probability of Observed or Fewer Deaths
Postpartum/HUB	1/773 (0.13%)	0	668	41.9%
Other Controlled Studies[2]	4/457 (0.88%)	1	334	20.7%

1 Control excludes subjects from placebo-controlled crossover safety Study VIT-06 since subjects who received placebo in Study VIT-06 also received FCM within ±7 days of the placebo dose.

2 Control group includes iron sucrose, oral iron, and placebo

2.6.7.5 Inferential Analyses for All Cause and Cardiac Mortality

Restricting the comparison of FCM to control in the randomized controlled trials reduces the bias on including data from non-controlled trials and supports a more objective comparison. The randomized controlled trials population provides an estimate of the intrinsic death rate and via randomization reduces systematic bias between treatments. This does not eliminate difficulties in interpretation since the rate difference is small and there are methodological challenges with combining medically disparate populations. The observed incidence rates in the randomized controlled trials for all cause mortality, all cause mortality within 30 days after the last dose of study drug, and cardiac mortality are small and the differences between treatment groups are also small as shown in **Table 87**. In addition, the 95% exact confidence intervals for the odds ratio of FCM versus control are wide for each observed mortality rate indicating substantial uncertainty regarding the existence of a mortality risk.

Table 87. Inferential Analysis for All Cause and Cardiac Mortality in Randomized Controlled Parallel-Group Trials

Mortality Endpoint	FCM Rate	Control Rate	Odds Ratio (CI)[1,2]	P-value[3]
All Cause	5/1230	1/1002	4.1 (0.5, 193.4)	0.2328
All Cause <30 days	4/1230	1/1002	3.3 (0.3, 161.0	0.3874
Cardiac	3/1230	1/1002	2.4 (0.2, 128.6)	0.6325

Includes Studies VIT-11, VIT-01, VIT-09, VIT-02/VIT-03, CL-15, CL-08, VIT-04, CL-02 and CARS
[1] Odds ratio for FCM vs. control (>1 indicates worse mortality for FCM)
[2] CI = Exact 95% confidence interval on odds ratio
[3] Fisher's exact test for FCM vs. Controls

In the FCM clinical program, 1 FCM subject died in the postpartum/HUB randomized controlled trials (RCTs), 4 FCM subjects and 1 control subject died in the other RCTs, and 5 FCM subjects died in the uncontrolled studies.

A complete analysis of deaths in the FCM clinical program, including individual case summaries and reviews of external, independent experts are presented in Appendix B.

2.6.7.6 Postpartum/HUB Trials

Details of the FCM subject who died in the postpartum/HUB RCT are presented in **Table 88**.

Table 88. Overview of FCM Death in Postpartum/HUB Randomized Controlled Trials (RCT)

Indication/ Study/ID/ Country	Investigator Assessment of Cause of Death	External, Independent Experts Assessments of Probable Cause of Death	Age/ Sex/ Race	Last dose of FCM -mg	Time since last dose -days
Postpartum/ VIT-01/ Case 1 RCT/ US	**Peripartum cardiomyopathy (PPCM) with heart failure, autopsy proven**	• *Current Illnesses:* obesity • *Past Hx*: multiparity, postpartum anemia with previous pregnancy • *Cause of death:* autopsy-confirmed peripartum dilated cardiomyopathy. Autopsy excluded AMI, valvular disease, hypersensitivity myocarditis & pulmonary embolus. • *Pathogenesis:* Idiopathic, early onset, often fatal. Frequency of death 6.4x greater in African Americans. Patient had the 3 strongest risk factors for PPCM, and the 3 strongest risk factors for fatal outcome of PPCM: African American, obese, multiparous x 4. • *Link to any iron agent, including FCM*: none, other iron related causes of dilated cardiomyopathy excluded. In preclinical toxicology studies, no adverse cardiac findings. • *Link to other trial deaths*: None	27/ F/ B	1,000	8

Bold= cases of probable cardiac etiology.

2.6.7.7 Other Randomized Controlled Trials (RCT)

Four deaths occurred in FCM-treated subjects and 1 death occurred in control-treated subjects in the other RCT.

FCM Subjects

- Three of the 4 deaths in the other RCT were in CKD subjects who have high baseline risk of death including 1 subject who received a total of only 200 mg FCM, and 1 who died >30 days following the last dose of FCM with advanced prostate cancer, bladder outlet obstruction, urosepsis, and withdrawal of resuscitative measures. One death resulted from a motor vehicle accident, 15 days after administration of 500 mg FCM.

- The total iron dose in 3 of the 4 FCM deaths was less than or equal to 1000 mg. The 1 exception was in a subject who died secondary to a motor vehicle accident, 15 days after the last 500 mg dose of study drug whose total calculated dose was 2000 mg.

An overview of deaths in FCM subjects in the other RCT is presented in **Table 89**.

Table 89. Overview of Deaths in FCM Subjects in Other Randomized Controlled Trials (RCT)

Indication/ Study/ID/ Country	Investigator Assessment of Cause of Death	External, Independent Experts Assessments of Probable Cause of Death	Age/ Sex/ Race	Last dose of FCM -mg	Time since last dose -days
Inflammatory Bowel Disease/ CL-08 Case 2 RCT/ Bulgaria	**Cardiac arrest, witnessed death**	• *Current illnesses:* ulcerative colitis, symptomatic aortic stenosis, mitral regurgitation, obesity • *Past Hx:* probable myocardial ischemia/angina • *Cause of death:* cardiac arrest in association with severe anemia (hemoglobin 4.8 g/dL one day prior to death) • *Pathogenesis:* Ischemia secondary to life threatening anemia in the setting of underlying valvular & ischemic heart disease • *Link to use of any iron agent, including FCM*: none • *Link to other trial deaths*: High co-morbidity	56/ M/ C	1,000	1 (26 hrs)
Hemodialysis dependent CKD/ CL-15/ Case 3 RCT/ Bulgaria	**Acute anterior myocardial infarction, documented in hospital**	• *Current Illnesses*: HD-CKD, diabetes x 14 years, diabetic nephropathy, retinopathy & neuropathy, HTN Grade III, chronic pyelonephritis. • *Cause of death:* documented acute extensive anterior myocardial infarction • *Pathogenesis*: acute blood loss (hemoglobin drop of 3.2g/dL 11.3→7.8 from 2 sources) resulting in a rapidly worsening anemia in the setting of presumed underlying CAD; suffered AMI, hospitalized with ST segment elevation x 4 d, tx'd without –lytics or angioplasty, arrested & died. 100-fold higher annual cardiovascular mortality rate than age matched population[66] • *Link to use of any iron agent, including FCM:* none • *Link to other trial deaths:* high co-morbidity	58/ M/ C	200	9 (AMI 4 days after first & only dose)
Non-dialysis dependent CKD/ VIT-04/ Case 4 RCT/ Australia	Multiple trauma s/p motor vehicle accident	• *Current Illnesses*: CKD, recurrent UTI, PVD, PUD, HTN, • *Past Hx*: s/p ruptured abdominal aortic • *Cause of death:* Trauma • *Pathogenesis:* Motor vehicle accident with no myocardial infarction or pulmonary embolism on autopsy • *Link to use of any iron agent, including FCM:* none • *Link to other trial deaths:* high co-morbidity	76/ M/ C	500	15
Non-dialysis dependent CKD/ VIT-04 Case 5 RCT/ US	Urosepsis with pneumonia, after being placed into hospice care	• *Current Illnesses*: CKD, CAD, HTN, atrial fibrillation, prostate cancer refractory to tx with hormone ablation (being treated with Casodex for advanced prostate cancer) • *Past Hx:* AMI, pneumonia • *Cause of death:* suffered fatal urosepsis secondary to bladder outlet obstruction • *Pathogenesis:* UTI complicated by bladder outlet obstruction 2^0 to prostate CA with pelvic radiation, in an elderly man with CAD. Course likely altered by family decision to not pursue aggressive treatment of Urosepsis when patient placed in hospice care. • *Link to use of any iron agent, including FCM*: none • *Link to other trial deaths:* high co-morbidity	85/ M/ C	1,000	35

Bold= cases of probably cardiac etiology.

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Control Subjects

One cardiovascular death (congestive heart failure) occurred in the control arm of Study CARS. An overview of the death in a control subject in the other RCT is presented in **Table 90**.

Table 90. Overview of Death in Control Subjects in Other Randomized Controlled Trials (RCTs)

Indication/ Study/ID/ Country	Investigator Assessment of Cause of Death	Major Pre-existing Conditions/Risk Factors Other than Anemia	Age/ Sex/ Race	Last dose of Iron Sucrose, (mg)	Time since last dose (days)
CHF CARS Case 1 Control RCT Russia	**Worsening Heart Failure**	• NDD-CKD • CHF NYHA Class IV • HTN • Angina, MI x3, • atrial fibrillation • thromboembolus of the pulmonary artery	72/ F/ C	200	5

Bold= cases of probable cardiac etiology.

2.6.7.8 Uncontrolled Clinical Trials

The remaining 5 deaths occurred in uncontrolled clinical trials. An overview of deaths in FCM subjects in the uncontrolled trials is presented in **Table 91**.

- Four of the 5 deaths in uncontrolled trials were in the high co-morbidity population, CKD subjects.
- Only 1 case was of presumed cardiac etiology.
- Two of the 5 deaths occurred much greater than 30 days following the last dose of FCM (98 and 46 days, respectively).
- Four of the 5 deaths followed a dose of ≤500 mg of FCM.

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Table 91. Overview of Deaths in FCM Subjects in Uncontrolled Trials

Indication/ Study/ID/ Country	Investigator Assessment of Cause of Death	External, Independent Experts Assessments of Probable Cause of Death	Age/ Sex/ Race	Last dose of FCM -mg	Time since last dose -days
Hemodialysis dependent CKD/ VIT-53214/ Case 1 Uncontrolled/ Romania	**Possible Heart Failure, unwitnessed death**	• *Past Hx:* HD-CKD, poorly controlled HTN, ischemic & uremic cardiomyopathy, LVH, chronic CHF-NYHA Class III with recent hospitalization, atrial fibrillation, pericarditis & anemia (hemoglobin 6mg/dL) • *Cause of death:* probable cardiovascular cause • *Pathogenesis:* Chronic CHF 2^0 to ischemic & uremic cardiomyopathy in the setting of chronic HD, anemic HD pts hospitalized with CHF have a 50% annual mortality rate • *Link to use of any iron agent, including FCM*: none • *Link to other trial deaths:* high co-morbidity	54/ F/ C	100	19
Hemodialysis dependent CKD/ VIT-53214/ Case 2 Uncontrolled/ Lithuania	Respiratory insufficiency (with progressive SOB & hypoxia during 14 day hospitalization) due to infiltrating pulmonary TB	• *Past Hx:* HD-CKD, active pulmonary TB with multiple hospitalizations to Tb hospitals, CAD, COPD, chronic persistent hepatitis • *Cause of death*: respiratory failure secondary to tuberculous pneumonia • *Pathogenesis:* Active TB in the setting of chronic lung disease & chronic heart, liver and kidney disease, in a patient undergoing chronic hemodialysis • *Link to use of any iron agent, including FCM:* none • *Link to other trial deaths:* high co-morbidity	59/ F/ C	200	15
Iron Deficiency Anemia/ VIT-06/ Case 3 Uncontrolled/ US	Pneumonia, respiratory failure, sepsis- positive sputum & blood cultures	• *Past Hx:* recurrent infections, depression on multiple psychotropic meds, seizures, gastric bypass for morbid obesity • *Cause of death:* Septic shock and acute respiratory failure secondary to *Aeromonas* pneumonia/septicemia • *Pathogenesis: Aeromonas* pneumonia in a patient with chronic illness, recurrent infections, & use of broad spectrum antibiotics. Independent cardiologist confirmed no AMI or CHF. • *Link to use of any iron agent, including FCM*: none • *Link to other trial deaths:* high co-morbidity	48/ F/ C	1,000	27
Non-dialysis dependent CKD/ VIT-05/ Case 4 Uncontrolled/ US	Colonic (Sigmoid) Perforation, surgically verified, diverticulitis perforation on pathology report	• *Past Hx*: CKD, diverticulosis, diverticulitis, DM type II, CAD, HTN, & previous hepatic abscess, • *Cause of death:* Colonic rupture with abdominal sepsis • *Pathogenesis:* Diverticulosis complicated by chronic bleeding, recurrent penetration, and acute perforation with peritonitis in an elderly man with coronary artery disease, chronic kidney disease and rheumatoid arthritis • *Link to use of any iron agent, including FCM:* none • *Link to other trial deaths:* high co-morbidity	86/ M/ C	500	98
Non-dialysis dependent CKD/ VIT-05/ Case 5 Uncontrolled/ US	Anoxic encephalopathy, GI bleeding	• *Past Hx:* CKD, DM type II, HTN, hyperlipidemia, chronic edema, recurrent UTIs • *Cause of death:* Massive GI bleeding after exploratory laparotomy • *Pathogenesis:* Anatomic site not identified, but this post-menopausal female patient suffered chronic GI bleeding manifested by recurrent iron deficiency anemia prior to fatal episode of bleeding early after laparatomy • *Link to use of any iron agent, including FCM:* none • *Link to other trial deaths:* high co-morbidity	64/ F/ C	500	46

Bold= cases of probable cardiac etiology.

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2.6.7.9 Mortality Summary

There was 1 death out of 1052 FCM-treated subjects in the postpartum/HUB population, 773 of which were in controlled studies. In all controlled clinical trials, including high and low risk populations, 5 deaths occurred in the FCM treated group and 1 in the comparator group. Three of the deaths (3/1230) in the FCM arm were likely of cardiac etiology (by different mechanisms dilated postpartum cardiomyopathy, myocardial infarction and cardiac arrest) vs. one (1/1002) in the control arm (congestive heart failure). Five deaths occurred in uncontrolled trials. Considering all controlled and uncontrolled studies combined, there were over twice as many subjects, with over twice the length of observation, with over twice as many high risk chronic kidney disease (CKD) patients treated with FCM compared to the control groups. The CKD population has a baseline annual mortality risk of 18.6% for hemodialysis and 7.5% for non-dialysis dependent CKD patients. These rates are much higher than for post-partum/HUB patients.

The potential predictive value of anaphylaxis, bioactive iron reactions, rate of hemoglobin rise, hemoglobin >13 g/dL, hypophosphatemia baseline mortality risk, and FCM dose on the mortality rate was explored. No death was consistent with the expected timing of anaphylaxis or bioactive iron reactions in relation to drug administration. No death was consistent with an allergic, anaphylactic, or bioactive iron reaction mechanism. Serious adverse event rates were associated with lower rather than higher observed hemoglobin levels, presumably reflecting the increased disease burden associated with serious anemia. The deaths occurred in subjects for whom the observed phosphate values at the time of the serious adverse event leading to death were not significantly low, or in subjects whose death occurred too early after FCM administration for hypophosphatemia to have developed. The overall observed mortality rate did not appear related to number of doses, total dose, maximum single dose and size of last administered dose. The observed interval between study drug administration and death is not compatible with the known toxicity of IV iron agents, the interval varied from 1 to 98 days and the pattern is not compatible with the known pharmacokinetic and pharmacodynamic characteristics of FCM.

A clear mechanism for the cause of death, unrelated to iron therapy, was established in 8 out of the 10 FCM treated cases. The remaining 2 deaths occurred in subjects with established pre-existing cardiac and other significant co-morbidities which are more than sufficient to explain these 2 deaths. These mechanisms of death share no pattern.

The mortality rate was related primarily to the baseline mortality risk of the clinical trial populations. That is, the mortality rate was highest in the HD and NDD-CKD populations and lowest in the postpartum and HUB populations.

The observed incidence rates in the randomized controlled trials for all cause mortality, all cause mortality within 30 days after the last dose of study drug, and cardiac mortality are small and within statistical expectation (Fishers exact p=0.2328, 0.3874 and 0.6325, respectively). There was a 42% probability of not observing a death in the control group in the postpartum/HUB population.

The heterogeneity of intrinsic mortality risk across populations and the low observed incidence rates of death within populations minimize the value of statistical comparisons and indicate the need for a thorough clinical review of each death to assess potential causality. The multiple external, independent experts drew the following conclusions about the individual deaths:

- No death was consistent with any known adverse effect of FCM or any intravenous iron agent at any dose or any rate of administration

- No death was consistent with any known pharmacokinetic and pharmacodynamic characteristics of FCM or any class of iron agent
- No deaths shared significant features with other deaths except for the frequent finding of a high comorbid disease burden that is characteristic of the study population
- No death lacked explanation

2.6.8 Safety Conclusions

Safety data from 3082 treated subjects, 2080 of whom were treated with FCM, demonstrate the comparative safety and tolerability of FCM vs. oral iron, iron sucrose, and placebo in both low risk (postpartum, HUB) and high risk (CKD, CHF) populations and safety data from the NDD-CKD population supports the long-term safety of repeat cycles (courses) of FCM. Although FCM is not intended as a chronic therapy in the postpartum and HUB populations, the safety of multiple course administration of FCM has been demonstrated in the NDD-CKD population.

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2.7 Risk Management Program

Luitpold will work with the FDA to determine the most appropriate Risk Management Program for the introduction of FCM into the marketplace. We are committed to heightened monitoring to provide assurance that the mortality imbalance is not related to FCM treatment and to identify and understand any risk as early as possible. We additionally plan to monitor reports of hypophosphotemia and work to understand any clinical implications of this event, quantifying risk factors to ultimately inform clinical guidance on patient management.

The proposed program will include:

1. A targeted product launch focused to a limited population of physicians that are equipped and experienced in the administration of IV iron;
2. A comprehensive physician education program concerning the product and the safety issues related to its use
3. A patient education program and the collection of adverse event and safety information above and beyond that collected via typical passive pharmacovigilance programs.

The goals and objectives listed below are designed to maximize the benefit of FCM in those patients who require the product the most while also minimizing the potential risks of taking FCM identified in the clinical trials, thereby maintaining a positive benefit risk balance.

2.7.1 Goals

1. To assure use of FCM in patients who have IDA secondary to postpartum or HUB who meet the following criteria:
    a. Need a more rapid and predictable recovery of hemoglobin than can be provided by oral iron,

    b. Have ongoing blood loss greater than the rate of repletion reasonably achievable with oral iron treatment;

    c. Require relief of anemia-related symptoms or dysfunction more rapidly than could be achieved by oral iron treatment or in patients intolerant or non-adherent with oral treatment regimens.
2. To assure that physicians and patients make well-informed decisions regarding the potential risks and benefits of using FCM as opposed to oral iron therapy.
3. To determine the short-term mortality risk in the postpartum and HUB populations meeting treatment criteria in patients treated and not treated with FCM.
4. To determine the incidence and risk factors for serious adverse events in the postpartum and HUB populations.

2.7.2 Objectives

1. To assure that an appropriate percentage of patients receiving FCM meet the clinical criteria for treatment by targeting education to designated providers regarding appropriate patient selection

2. To assure that an appropriate percentage of prescribers and patients understand the benefits and risks of FCM therapy as opposed to oral iron so that an informed benefit risk decision can be made
3. To provide quantitative data on the incidence of serious adverse events, including deaths in patients receiving FCM in the approved indications until data are available on at least 10,000 patients

2.7.3 Risk Management Program Strategies and Tools

Given the goals and objectives listed above, and with agreement from the FDA, the following strategies and tools will be implemented following the approval of FCM: Dear Healthcare Professional Letters, Physician Education Programs, Patient Education Programs, Medication Guides, Disease Registry, and follow-up surveys. The table below shows the relationship between the objectives, tools and evaluation.

Relationship Between Risk Management Program Objectives, Tools, and Evaluation		
Objective	**Tool**	**Evaluation**
Appropriate physician selection Ensure that FCM is administered by qualified and informed physicians.	Targeted Product Launch	IMS or Verispan Data compared to enrollment data Utilization study
	Physician Education Materials	
	Dear Doctor Letters	
	CME Programs	
Ensure appropriate patient selection by limiting prescribing to patients with PP and HUB	Labeling (Package Insert)	Patient Survey
Ensure that physicians and patients are informed about both benefits and risks so that an informed benefit risk decision can be made.	Focused prescribing information	Physician survey Patient survey
	Physician Educational Materials	
	Dear Doctor Letters	
	Patient Educational Materials	Registry
	Medication Guide	
	CME Programs	
Educate patients to recognize the onset of an adverse event and how to seek immediate evaluation and treatment.	Patient Educational Materials	Patient Survey
	Medication Guides	Registry
Educate prescribers, patients and their families to know how to report the event.	Physician Educational Materials	Physician Survey
	Patient Education Materials	Patient Surveys Registry
	Medication Guides	Cross Reference National Death Index
Collect information on safety and patient outcomes	Post-approval safety studies, including the ongoing randomized and controlled trials, Disease Registry and potential studies using existing EMR or claims databases	Registry
	Pharmacovigilance Plan and AE Reports	
	Patient Surveys	

2.7.4 Targeted Product Launch

Luitpold has significant experience in the marketing of IV iron products since the launch of Dexferrum® (iron dextran injection, USP) in 1996 and Venofer® (iron sucrose injection, USP) in 2000. We are very conservative in our marketing practices, focusing the efforts of our national sales force (35 Sales Representatives and 12 Clinical Support Specialists) on marketing our products only within the FDA approved indications. Documented Standard Operating Procedures and our Corporate Compliance Program mandate that all Luitpold employees work ethically within the PhRMA Guidelines, FDA regulations, and all legal requirements. Luitpold in fact has never received a FDA Warning Letter, had advertising pulled from distribution, or had any deficiency noted upon any FDA inspection relating to pharmacovigilance issues. Our launch of FCM will be in keeping with our policy to comply with all FDA requirements to the fullest extent.

Market research has identified that FCM will be administered primarily by hematologists, hematologists/oncologists and internists practicing in hospitals, infusion centers and clinics appropriately staffed and equipped to administer IV products. These physicians are already familiar with the administration of IV iron through their experience with iron dextran and iron sucrose and are able to respond to the serious adverse events associated with the 1st and 2nd generation IV iron products. Our initial marketing efforts will be focused on those physicians who will be administering FCM. Afterwards we will expand our focus to include the education of OB/GYNs that will act as a referral base to those, first tier, previously targeted physicians, who already are experienced with FCM administration. Luitpold has never initiated any product specific, direct to consumer advertising programs and would commit not to do so with FCM for the first three years after the launch of FCM (in compliance with PhRMA Guidelines) or upon completion and successful review of the data collected in this Program.

2.7.5 Physician Education Program

Luitpold is committed to an extensive Physician Education program upon the launch of FCM. This program will utilize letters to targeted physicians, CME programs and other medical education materials to ensure that physicians are informed about both the benefits and risks of FCM treatment so that an informed treatment decision can be made.

Upon the launch of FCM, letters to the targeted physicians will be sent making them aware of the product, its benefits / risks and introducing components of the Risk Management Program. Additionally the letter will focus on proper patient selection as delineated by FCMs approved indications, contraindications, and precautions.

CME programs have played a major part of the Physician and other professional healthcare provider education programs for Luitpold's existing injectable iron products. Currently Luitpold is the sponsor of CME and non-CME programs that center around our currently approved products indicated for the treatment of iron deficiency anemia in general (Dexferrum®) and iron deficiency anemia in dialysis and non-dialysis dependent CKD patients with Venofer®. These programs include both complimentary on-line and lecture based programs. To obtain the CME/CE credits, course objectives are clearly defined and post program evaluations are utilized to ensure the understanding of key concepts. Luitpold will continue to sponsor CME/CE programs and develop specific programs that are focused on FCM. Modules within these programs will cover such topics as appropriate patient selection, proper dosing, precautions,

known adverse reactions and the reporting of adverse reactions to Luitpold's pharmacovigilance group.

Luitpold will also train its sales force to properly educate targeted medical providers discussed above on all of the therapies available for use in the targeted population (such as oral iron) and, as to FCM, educate them only on the labeled uses of the product.

They will concentrate on the use of the products in patients with IDA secondary to postpartum or HUB who:

1. Need a more rapid and predictable recovery of hemoglobin than can be provided by oral iron,
2. Have ongoing blood loss greater than the rate of repletion reasonably achievable with oral iron treatment;
3. Require relief of anemia-related symptoms or dysfunction more rapidly than could be achieved by oral iron treatment or in patients intolerant or non-adherent with oral treatment regimens.

Key messages to providers will come from the approved package insert and include proper patient identification, dosing, contraindications, precautions and known adverse reactions. These messages will be enhanced by educational prompts such as laminated dosing cards and brochures discussing hypophosphotemia and iron deficiency anemia.

In addition to our sales force, Luitpold will develop a group of Medical Professional Liaisons and Clinical Specialists (nurse experts in the administration of IV iron) who will make presentations to targeted physician providers and their staff on the proper use of FCM. They will encourage reporting of all adverse reactions relating to the product.

Off label uses and dosing will be discouraged by our staff. Any unsolicited communications on off label uses will be directed to our Medical Affairs or Professional Services Departments via a 24 hour toll free phone number as required by existing SOPs. These departments are staffed by licensed Physicians and Pharmacists who will actively monitor such calls and provide trend analysis so that corrective action can be taken as necessary.

2.7.6 Patient Education Program

Patients must be educated about the benefits and the risks associated with FCM and they must be aware of the signs and symptoms of adverse events so that they may seek early evaluation and treatment, and thereby reduce the risks of serious outcomes should they experience such an event. Medication guides that outline the risks and contraindications with regard to FCM will be made available for distribution to each patient. Given that current medication guides are essentially risk documents, additional patient education that includes benefits is critical to the physician/patient interaction in making an informed benefit risk decision. Educational material will be developed in an iterative process using input from testing in a diverse sample of patients in order to assure that the key messages are effectively communicated. In addition, a survey will be conducted on a sample of patients following treatment with FCM, to assess their knowledge and understanding of the key messages of the patient education program.

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2.7.7 Collection of Adverse Event Data

Luitpold Pharmaceuticals maintains a comprehensive pharmacovigilance program that actively collects Adverse Event reports. Reports are received by Luitpold's Safety Associates (nurses with specific training in event collection and reporting) and reviewed by a licensed physician prior to finalization. The reports are then entered into our pharmacovigilance database and reported to regulatory authorities and our European marketing partner. Luitpold maintains a close relationship with our European partner who maintains the Global Pharmacovigilance database. Event signaling / trending is performed on both a global and US specific safety databases. Targeted follow-up will be initiated for any deaths or cases of hypophosphatemia or serious allergic / hypersensitivity reactions. Special targeted follow-up data collection instruments will be developed to gather relevant information at the time of the initial report to maximize the likelihood of obtaining all of the information necessary to evaluate these events.

2.7.8 Additional Studies

Luitpold is committed to the continued study of FCM in our current proposed indications and in other populations suffering from IDA through clinical and epidemiological studies.

2.7.8.1 Clinical studies

In anticipation of a post approval requirement, we have already initiated two prospective, controlled studies continuing to investigate the safety of the 1000mg single FCM dose in patients with IDA secondary to postpartum / HUB or nondialysis dependent / hemodialysis dependent CKD. These two studies will randomize 1500 patients to FCM or standard of care identified by the investigator and follow adverse events for 30 days post treatment. As discussed within this document, we have also completed two studies in patients with IDA associated with non-dialysis dependent chronic kidney disease and look forward to initiating future studies in other anemic populations.

2.7.8.2 Epidemiology safety study

Luitpold is also committed to conducting a post-approval study to quantify the rate of serious adverse events and deaths in a large population receiving FCM and a similar comparison population. We propose a cohort study (disease registry) to include prospective data collection on all patients treated in selected clinical sites such as hematologists and infusion centers. We will target to a sample size sufficiently large to provide reassurance regarding mortality and serious clinical consequences of hypophosphatemia. We are prepared to discuss with the FDA appropriate strategies for this study (registry), including the sample size, the selection of the comparison group, and methods for analysis. Current plans include the identification of key sentinel sites that would actively collect data on all patients receiving FCM, including selected baseline characteristics, and medical outcomes associated with the treatment of IDA in female patients indicated for treatment with FCM. Outcomes would be collected by the sites, and also through linkage to the mortality and cause of death data from the National Death Index. Data would be analyzed semi-annually to assess rates of events of special interest overall, and, as the utilization increases, by population subgroups and potential risk factors. Comparisons with an appropriate non-FCM population would be made, adjusting for difference in baseline risk, to

address issues of confounding by indication for treatment. Prior to the implementation of this study, a research protocol and analysis plan will be developed and reviewed with FDA.

This study would provide faster event reporting than can be obtained from prospective clinical trials given the size requirements for such trials based on very small event rates. Additionally, this initiative would provide faster, more accurate, event reporting than can be obtained simply from passive pharmacovigilance programs. Any serious events of special interest would be immediately reviewed, providing complete information regarding the event to Luitpold and the FDA.

2.7.9 Program Evaluation

A critical aspect of any Risk Management Program is the evaluation component. Fundamentally, the evaluation component of the Risk Management Program relates to the measurement of established metrics to determine how effectively the Risk Management Program is in meeting its stated goals and objectives. For FCM, the primary focus will be on metrics pertaining to safety events negotiated with the FDA as discussed above. In addition, we will capture information on the effectiveness of the Risk Management Program as follows:

Surveys will be conducted to assess the effectiveness of the education programs in communicating the key messages to physicians about the importance of appropriate patient selection and about risks and benefits, and to assess patients understanding of the risks and benefits of FCM.

Information from market research sources, such as IMS and potentially the claims and electronic medical record (EMR) data will be used to evaluate utilization pattern as follows:

1. Distribution of providers by specialty, geographic location and clinical practice type to compare with the distribution targeted by the FCM Risk Management Plan.
2. Percentage of patients receiving FCM who meet the patient selection criteria.

Should Luitpold determine the utilization is not meeting the objectives of the Risk Management Program, we will evaluate the root cause of the deviations and develop appropriate intervention strategies. Potential interventional strategies could include providing new educational materials, revised CME programs and sending representatives, Medical Professional Liaisons and Clinical Specialists specifically to locations when there is identified non-compliance with goals of the RMP.

2.8 Medical Benefit Risk Assessment

Choosing among iron products for the treatment of IDA for an individual patient requires gauging the likelihood of treatment success and the consequences of treatment failure. This assessment must be made in the context of the need for rapid clinical effect, ease of adherence and the differential risks of the various therapies. Treatment failure leaves patients prone to prolonged anemia-related clinical consequences including heightened risk of intervention by RBC transfusion. Treatment success results in increased Hb levels, preferably within the normal range for the population. Comparisons of effectiveness of the treatment, patient adherence to treatment, and the safety/tolerability across iron treatment options are described below.

2.8.1 Benefits

Clinical efficacy:

FCM vs. Oral Iron

There is a treatment advantage of FCM over oral iron. Anemic postpartum and HUB patients treated with FCM achieved both, greater and earlier resolution of anemia (Hb >12 g/dL), than oral iron treated patients. More FCM-treated patients achieved both, greater and earlier Hb increases (>3 g/dL), than with oral iron. FCM replenished iron stores (ferritin change from baseline: 175-226 ng/mL) after a single course of FCM while oral iron did not (ferritin change from baseline: 3-17 ng/mL) after 6 weeks of three times a day oral iron therapy. The clinical benefit of FCM over oral iron was observed across demographic and baseline characteristics. Thus, FCM is an effective agent that is superior to oral iron for the treatment of IDA in postpartum and HUB subjects.

FCM vs. other IV Irons

At this time, there is no efficacy data from randomized controlled trials comparing FCM vs. other IV iron agents. Second generations irons are not approved for use in this population. As currently labeled, use of iron dextran would require more than 16 infusions, each requiring personnel equipped and trained for resuscitation of anaphylaxis. However, if dosage and administration characteristics (infusion time and number of infusions) are adjusted for, it is not expected that there would be a significant difference between FCM and other IV iron agents in terms of achieving greater and earlier Hb increases.

Adherence:

FCM vs. Oral Iron

FCM provides a fundamental benefit in terms of adherence compared to oral iron. In approximately 92% of patients, only 1 or 2 administration(s) was needed. That means almost all patients received their entire calculated dose of iron supplementation in 7 days instead of having to adhere to oral iron three times a day for 42 days to complete their oral iron course.

In fact, the adherence benefit of FCM over oral iron is probably underestimated in the clinical trial because of the expected high rate of adherence of patients taking oral iron in the controlled setting of a clinical trial. High adherence was expected for the intravenous products since

treatment is administered directly by site personnel, but the high adherence to oral iron in the program was not consistent with reports from clinical practice. In the absence of clinical trial encouragement, non-adherence to oral iron therapy approaches 40%.[14]

FCM can also be administered immediately upon determination of the clinical need with less clinical supervision time (eg., short infusion time). The FCM dose of 15 mg/kg up to a maximum of 1000 mg permits correction of anemia and replenishment of iron stores in 1-2 doses in approximately 92% of postpartum and HUB patients. For women with difficulties accessing healthcare, this is an important benefit.

FCM vs. Other IV Irons

To be treated with iron dextran, the only approved intravenous iron agent for IDA, the anemic postpartum and HUB patient would need to be informed and to accept anaphylactic risk that is independent of rate or dose of administration and may occur despite a successful test dose. Administration of currently available 2nd generation IV iron agents in this population would be outside of the current labeled indications and would require multiple doses with prolonged intravenous infusion time. Thus, FCM would be a more acceptable and convenient therapeutic option than currently available IV iron agents.

2.8.2 Risk

FCM vs. Oral iron

The profile of adverse events was generally similar between the FCM and oral iron groups in the postpartum and HUB populations. Notable treatment group differences (**Table 39**) included a higher incidence of gastrointestinal disorders in the oral iron group (29.9%) compared to the FCM group (11.9%), while the incidence of adverse events associated with skin and subcutaneous tissue disorders was higher in the FCM group (6.6%) compared to the oral iron group (2.5%). Among the adverse events associated with skin and subcutaneous tissue disorders, a greater proportion of FCM subjects experienced rash (2.2%) than oral iron subjects (1.3%). In most cases the rashes were mild and not indicative of an allergic reaction to FCM. Similar results were seen in oral iron controlled studies that also included the NDD-CKD and IBD populations (**Table 50**).

Transient, asymptomatic decreases in serum phosphate were observed in both FCM and oral iron subjects, but the decreases did not result in adverse events or serious adverse events. Phosphate experts who have reviewed this data consider the decrease in phosphate to be interesting but clinically not important in the postpartum and HUB populations.

FCM vs. Other IV Irons

The profile of adverse events was generally similar between the FCM and iron sucrose groups. Notable differences between the treatment groups (**Table 54**) were for the incidences of gastrointestinal disorders and nervous system disorders, which were higher in the iron sucrose group compared to the FCM group.

Adverse Events

Few subjects discontinued due to adverse events (<2% in PP/HUB, oral iron controlled, and iron sucrose controlled studies). The events tended to be associated with skin and subcutaneous tissue

disorders in the FCM group and gastrointestinal disorders in the oral iron group. There was no clear pattern of differences between the FCM and iron sucrose groups.

A review of the safety profile of all iron treatments in the program shows that risk of serious adverse events was generally similar across all treatments: FCM, oral iron, and iron sucrose. No clinically important increase in the risk of hypotension, potential allergic reactions, bioactive iron reactions, infections, or serious ischemic cardiovascular events was observed for FCM compared to oral iron or iron sucrose. Neither the size of the single and total dose of FCM nor the maximum Hb obtained after treatment were associated with an increased risk of serious adverse events.

Mortality

A review of the mortality data by external, independent experts concluded no connection between FCM and mortality. The most likely explanation for the excess of deaths in the FCM group is related to statistical variability and instability relating to the observation of infrequent events. Nevertheless, Luitpold is proposing a risk management approach that limits the launch of FCM to a targeted population of physicians and enables the real time monitoring and collection of data to better quantify the mortality risks in users of FCM and a similar population not receiving FCM. While details of this program will be finalized with FDA, Luitpold proposes that data should be collected on at least 10,000 patients. This effort will be supplemented by educational programs for both physicians and patients.

2.8.3 Benefit/Risk Summary:

FCM provided earlier correction of anemia and higher Hb levels than did oral iron in the HUB and postpartum populations with fewer infusions than would be required for other intravenous iron products. The safety and tolerability profile for FCM was similar to that of oral iron and iron sucrose with no serious hypersensitivity, no symptomatic hypotension, and no constellation of bioactive iron reactions. Furthermore, it is safer and more tolerable at higher doses than possible with other intravenous iron agents, therefore allowing more practical dosing. FCM provides substantial benefits over current iron treatments without their dosing limitations and safety risks. The ability to correct anemia with one to three infusions provides an important advantage in terms of adherence to treatment. On balance, FCM availability will reduce barriers to treatment for postpartum and HUB patients, provide a more practical and rapid treatment than existing therapies, and do so without increasing the risks of treatment for these patients.

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Appendix A

Supporting Statistical Tables

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Luitpold Pharmaceuticals, Inc.
FCM
Revised Label for Postpartum and Heavy Uterine Bleeding

Table 5.2.1.1AC
Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group
(All Post-Partum and HUB Studies)
Safety Population

			Crossover Study	
	FCM (N= 773)	Oral Iron (N= 668)	FCM (N= 279)	Placebo (N= 263)
AT LEAST ONE ADVERSE EVENT	367 (47.5%)	355 (53.1%)	66 (23.7%)	36 (13.7%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	3 (0.4%)	1 (0.1%)	1 (0.4%)	0 (0.0%)
LEUKOPENIA	2 (0.3%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
LYMPHADENOPATHY	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
THROMBOCYTHAEMIA	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
CARDIAC DISORDERS	5 (0.6%)	3 (0.4%)	0 (0.0%)	1 (0.4%)
BUNDLE BRANCH BLOCK LEFT	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CARDIAC FAILURE	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CARDIAC FAILURE CONGESTIVE	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
CARDIAC FLUTTER	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
MITRAL VALVE PROLAPSE	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PALPITATIONS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
TACHYCARDIA	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
EAR AND LABYRINTH DISORDERS	3 (0.4%)	5 (0.7%)	0 (0.0%)	0 (0.0%)
EAR DISORDER	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
EAR PAIN	1 (0.1%)	3 (0.4%)	0 (0.0%)	0 (0.0%)
VERTIGO	1 (0.1%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
ENDOCRINE DISORDERS	0 (0.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
GOITRE	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
HYPOTHYROIDISM	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
EYE DISORDERS	1 (0.1%)	1 (0.1%)	1 (0.4%)	0 (0.0%)

Note: All Post-partum and HUB Studies: VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-6011.
Placebo Controlled, Single-Dose Crossover Study: VIT-5006.
Treatment Emergent Adverse Events for 7 days following the First Dose for Placebo Controlled, Single-Dose Crossover Study: VIT-5006.
Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.

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Table 5.2.1.1AC
Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group
(All Post-Partum and HUB Studies)
Safety Population

	FCM (N= 773)	Oral Iron (N= 668)	Crossover Study FCM (N= 279)	Crossover Study Placebo (N= 263)
CONJUNCTIVITIS	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
LACRIMATION INCREASED	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
VISION BLURRED	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
GASTROINTESTINAL DISORDERS	92 (11.9%)	200 (29.9%)	15 (5.4%)	11 (4.2%)
ABDOMINAL DISCOMFORT	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
ABDOMINAL DISTENSION	0 (0.0%)	6 (0.9%)	0 (0.0%)	0 (0.0%)
ABDOMINAL PAIN	20 (2.6%)	13 (1.9%)	2 (0.7%)	0 (0.0%)
ABDOMINAL PAIN LOWER	5 (0.6%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
ABDOMINAL PAIN UPPER	11 (1.4%)	10 (1.5%)	0 (0.0%)	0 (0.0%)
ABDOMINAL TENDERNESS	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
ANAL FISTULA	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
APHTHOUS STOMATITIS	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
CONSTIPATION	18 (2.3%)	86 (12.9%)	3 (1.1%)	2 (0.8%)
DIARRHOEA	12 (1.6%)	25 (3.7%)	1 (0.4%)	3 (1.1%)
DRY MOUTH	1 (0.1%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
DYSPEPSIA	3 (0.4%)	7 (1.0%)	2 (0.7%)	1 (0.4%)
FAECES DISCOLOURED	0 (0.0%)	8 (1.2%)	0 (0.0%)	0 (0.0%)
FAECES HARD	0 (0.0%)	3 (0.4%)	0 (0.0%)	0 (0.0%)
FLATULENCE	5 (0.6%)	5 (0.7%)	0 (0.0%)	0 (0.0%)
FOOD POISONING	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
GASTRIC ULCER	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GASTRITIS	1 (0.1%)	4 (0.6%)	1 (0.4%)	0 (0.0%)
GASTROINTESTINAL DISCOMFORT	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GASTROINTESTINAL PAIN	0 (0.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
GASTROOESOPHAGEAL REFLUX DISEASE	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)

Note: All Post-partum and HUB Studies: VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-6011.
Placebo Controlled, Single-Dose Crossover Study: VIT-5006.
Treatment Emergent Adverse Events for 7 days following the First Dose for Placebo Controlled, Single-Dose Crossover Study: VIT-5006.
Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.

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Table 5.2.1.1AC
Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group
(All Post-Partum and HUB Studies)
Safety Population

	FCM (N= 773)	Oral Iron (N= 668)	Crossover Study FCM (N= 279)	Crossover Study Placebo (N= 263)
HAEMORRHOIDS	1 (0.1%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
INFREQUENT BOWEL MOVEMENTS	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
IRRITABLE BOWEL SYNDROME	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
LOOSE STOOLS	1 (0.1%)	4 (0.6%)	0 (0.0%)	1 (0.4%)
NAUSEA	18 (2.3%)	54 (8.1%)	7 (2.5%)	4 (1.5%)
ODYNOPHAGIA	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
STOMACH DISCOMFORT	1 (0.1%)	5 (0.7%)	0 (0.0%)	0 (0.0%)
TOOTHACHE	5 (0.6%)	5 (0.7%)	0 (0.0%)	0 (0.0%)
VOMITING	7 (0.9%)	17 (2.5%)	0 (0.0%)	0 (0.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	83 (10.7%)	28 (4.2%)	11 (3.9%)	5 (1.9%)
APPLICATION SITE ERYTHEMA	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
APPLICATION SITE INFLAMMATION	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
APPLICATION SITE OEDEMA	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
APPLICATION SITE PARAESTHESIA	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ASTHENIA	4 (0.5%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
BLOODY DISCHARGE	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
BODY TEMPERATURE INCREASED	3 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CHEST DISCOMFORT	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CHEST PAIN	5 (0.6%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
CHILLS	3 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
FATIGUE	14 (1.8%)	7 (1.0%)	1 (0.4%)	0 (0.0%)
FEELING COLD	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
HANGOVER	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
INFLUENZA LIKE ILLNESS	2 (0.3%)	1 (0.1%)	0 (0.0%)	1 (0.4%)

Note: All Post-partum and HUB Studies: VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-6011.
Placebo Controlled, Single-Dose Crossover Study: VIT-5006.
Treatment Emergent Adverse Events for 7 days following the First Dose for Placebo Controlled, Single-Dose Crossover Study: VIT-5006.
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Table 5.2.1.1AC
Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group
(All Post-Partum and HUB Studies)
Safety Population

	FCM (N= 773)	Oral Iron (N= 668)	Crossover Study FCM (N= 279)	Crossover Study Placebo (N= 263)
INFUSION SITE BRUISING	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INFUSION SITE BURNING	7 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INFUSION SITE OEDEMA	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INFUSION SITE PAIN	6 (0.8%)	0 (0.0%)	1 (0.4%)	1 (0.4%)
INFUSION SITE PRURITUS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INFUSION SITE RASH	0 (0.0%)	0 (0.0%)	2 (0.7%)	0 (0.0%)
INFUSION SITE REACTION	5 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INFUSION SITE SWELLING	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INFUSION SITE WARMTH	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INJECTION SITE BRUISING	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INJECTION SITE ERYTHEMA	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INJECTION SITE EXTRAVASATION	3 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INJECTION SITE HAEMORRHAGE	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.4%)
INJECTION SITE PARAESTHESIA	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INJECTION SITE REACTION	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INJECTION SITE URTICARIA	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
LOCAL SWELLING	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MALAISE	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
OEDEMA	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
OEDEMA PERIPHERAL	6 (0.8%)	4 (0.6%)	0 (0.0%)	0 (0.0%)
PAIN	7 (0.9%)	3 (0.4%)	0 (0.0%)	1 (0.4%)
PYREXIA	13 (1.7%)	9 (1.3%)	3 (1.1%)	1 (0.4%)
RIGORS	3 (0.4%)	1 (0.1%)	1 (0.4%)	0 (0.0%)
THIRST	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
VENIPUNCTURE SITE HAEMORRHAGE	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: All Post-partum and HUB Studies: VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-6011.
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Table 5.2.1.1AC
Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group
(All Post-Partum and HUB Studies)
Safety Population

	FCM (N= 773)	Oral Iron (N= 668)	Crossover Study FCM (N= 279)	Crossover Study Placebo (N= 263)
HEPATOBILIARY DISORDERS	3 (0.4%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
BILE DUCT STONE	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CHOLECYSTITIS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CHOLECYSTITIS ACUTE	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CHOLELITHIASIS	2 (0.3%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
IMMUNE SYSTEM DISORDERS	3 (0.4%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
FOOD ALLERGY	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HYPERSENSITIVITY	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
INFECTIONS AND INFESTATIONS	108 (14.0%)	90 (13.5%)	9 (3.2%)	11 (4.2%)
APPENDICITIS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
BREAST ABSCESS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
BRONCHIAL INFECTION	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
BRONCHITIS	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
BRONCHITIS ACUTE	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CANDIDIASIS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CELLULITIS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CONDYLOMA ACUMINATUM	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CYSTITIS	3 (0.4%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
DENTAL CARIES	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
EAR INFECTION	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
ENDOMETRITIS	1 (0.1%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
ENDOMETRITIS DECIDUAL	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ENTEROVIRUS INFECTION	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
ESCHERICHIA INFECTION	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: All Post-partum and HUB Studies: VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-6011.
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Luitpold Pharmaceuticals, Inc.
FCM
Revised Label for Postpartum and Heavy Uterine Bleeding

Table 5.2.1.1AC
Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group
(All Post-Partum and HUB Studies)
Safety Population

	FCM (N= 773)	Oral Iron (N= 668)	Crossover Study FCM (N= 279)	Crossover Study Placebo (N= 263)
FUNGAL INFECTION	0 (0.0%)	2 (0.3%)	2 (0.7%)	0 (0.0%)
GASTROENTERITIS	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
GASTROENTERITIS VIRAL	3 (0.4%)	5 (0.7%)	0 (0.0%)	0 (0.0%)
HELICOBACTER GASTRITIS	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
HEPATITIS A	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HERPES SIMPLEX	2 (0.3%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
INFECTION	0 (0.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
INFLUENZA	8 (1.0%)	5 (0.7%)	0 (0.0%)	3 (1.1%)
KIDNEY INFECTION	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
LABYRINTHITIS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
LARYNGITIS	0 (0.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
LARYNGOTRACHEITIS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MASTITIS	6 (0.8%)	5 (0.7%)	1 (0.4%)	2 (0.8%)
NASOPHARYNGITIS	18 (2.3%)	21 (3.1%)	3 (1.1%)	2 (0.8%)
OTITIS EXTERNA	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
OTITIS MEDIA	0 (0.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
OTITIS MEDIA ACUTE	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
PELVIC ABSCESS	0 (0.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
PELVIC INFLAMMATORY DISEASE	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PHARYNGITIS	3 (0.4%)	4 (0.6%)	0 (0.0%)	0 (0.0%)
PHARYNGITIS STREPTOCOCCAL	3 (0.4%)	1 (0.1%)	0 (0.0%)	1 (0.4%)
PHARYNGOTONSILLITIS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PILONIDAL CYST	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PNEUMONIA	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
POST PROCEDURAL CELLULITIS	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
POSTOPERATIVE INFECTION	2 (0.3%)	2 (0.3%)	0 (0.0%)	0 (0.0%)

Note: All Post-partum and HUB Studies: VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-6011.
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Table 5.2.1.1AC
Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group
(All Post-Partum and HUB Studies)
Safety Population

	FCM (N= 773)	Oral Iron (N= 668)	Crossover Study FCM (N= 279)	Crossover Study Placebo (N= 263)
POSTPARTUM SEPSIS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PYELONEPHRITIS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
RESPIRATORY TRACT INFECTION	3 (0.4%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
RHINITIS	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SEPSIS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SINUSITIS	10 (1.3%)	8 (1.2%)	1 (0.4%)	0 (0.0%)
SKIN CANDIDA	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TOOTH ABSCESS	4 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TOOTH INFECTION	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
UPPER RESPIRATORY TRACT INFECTION	11 (1.4%)	9 (1.3%)	0 (0.0%)	1 (0.4%)
URINARY TRACT INFECTION	9 (1.2%)	12 (1.8%)	0 (0.0%)	2 (0.8%)
VAGINAL INFECTION	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
VAGINAL MYCOSIS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
VAGINITIS	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
VAGINITIS BACTERIAL	1 (0.1%)	1 (0.1%)	1 (0.4%)	0 (0.0%)
VIRAL INFECTION	0 (0.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
VIRAL UPPER RESPIRATORY TRACT INFECTION	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
VULVOVAGINITIS TRICHOMONAL	0 (0.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	13 (1.7%)	12 (1.8%)	0 (0.0%)	0 (0.0%)
ARTHROPOD BITE	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ARTHROPOD STING	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
BURNS SECOND DEGREE	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CONTUSION	3 (0.4%)	2 (0.3%)	0 (0.0%)	0 (0.0%)

Note: All Post-partum and HUB Studies: VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-6011.
Placebo Controlled, Single-Dose Crossover Study: VIT-5006.
Treatment Emergent Adverse Events for 7 days following the First Dose for Placebo Controlled, Single-Dose Crossover Study: VIT-5006.
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Table 5.2.1.1AC
Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group
(All Post-Partum and HUB Studies)
Safety Population

	FCM (N= 773)	Oral Iron (N= 668)	Crossover Study FCM (N= 279)	Crossover Study Placebo (N= 263)
HEAD INJURY	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INCISION SITE COMPLICATION	3 (0.4%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
INCISION SITE HAEMORRHAGE	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
JOINT INJURY	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
JOINT SPRAIN	0 (0.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
MUSCLE STRAIN	2 (0.3%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
POST PROCEDURAL DISCHARGE	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
SKIN LACERATION	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
SUNBURN	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
THERMAL BURN	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
INVESTIGATIONS	52 (6.7%)	27 (4.0%)	4 (1.4%)	2 (0.8%)
ALANINE AMINOTRANSFERASE	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
ALANINE AMINOTRANSFERASE INCREASED	11 (1.4%)	15 (2.2%)	2 (0.7%)	0 (0.0%)
ASPARTATE AMINOTRANSFERASE	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
ASPARTATE AMINOTRANSFERASE INCREASED	7 (0.9%)	10 (1.5%)	2 (0.7%)	0 (0.0%)
BASOPHIL COUNT INCREASED	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
BLOOD ALKALINE PHOSPHATASE INCREASED	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
BLOOD BILIRUBIN INCREASED	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
BLOOD CALCIUM DECREASED	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
BLOOD GLUCOSE DECREASED	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
BLOOD GLUCOSE INCREASED	0 (0.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
BLOOD LACTATE DEHYDROGENASE INCREASED	2 (0.3%)	1 (0.1%)	0 (0.0%)	1 (0.4%)
BLOOD PHOSPHORUS DECREASED	26 (3.4%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
BLOOD POTASSIUM DECREASED	4 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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(All Post-Partum and HUB Studies)
Safety Population

			Crossover Study	
	FCM (N= 773)	Oral Iron (N= 668)	FCM (N= 279)	Placebo (N= 263)
BLOOD POTASSIUM INCREASED	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
BLOOD SODIUM INCREASED	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
BLOOD THYROID STIMULATING HORMONE INCREASED	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
BLOOD UREA DECREASED	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
C-REACTIVE PROTEIN INCREASED	4 (0.5%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
CARDIAC MURMUR	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
ELECTROCARDIOGRAM ABNORMAL	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
GAMMA-GLUTAMYLTRANSFERASE ABNORMAL	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	7 (0.9%)	2 (0.3%)	1 (0.4%)	0 (0.0%)
HEART RATE INCREASED	2 (0.3%)	1 (0.1%)	1 (0.4%)	0 (0.0%)
HEART RATE IRREGULAR	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.4%)
HEPATIC ENZYME INCREASED	2 (0.3%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
LIVER FUNCTION TEST ABNORMAL	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
RED CELL DISTRIBUTION WIDTH INCREASED	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SMEAR CERVIX ABNORMAL	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
WEIGHT INCREASED	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
WHITE BLOOD CELL COUNT INCREASED	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
METABOLISM AND NUTRITION DISORDERS	3 (0.4%)	7 (1.0%)	0 (0.0%)	0 (0.0%)
ANOREXIA	0 (0.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
DECREASED APPETITE	0 (0.0%)	3 (0.4%)	0 (0.0%)	0 (0.0%)
FLUID RETENTION	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HYPERGLYCAEMIA	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
HYPERLIPIDAEMIA	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)

Note: All Post-partum and HUB Studies: VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-6011.
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(All Post-Partum and HUB Studies)
Safety Population

	FCM (N= 773)	Oral Iron (N= 668)	Crossover Study FCM (N= 279)	Crossover Study Placebo (N= 263)
HYPOGLYCAEMIA	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HYPOKALAEMIA	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	38 (4.9%)	26 (3.9%)	7 (2.5%)	3 (1.1%)
ARTHRALGIA	10 (1.3%)	7 (1.0%)	1 (0.4%)	0 (0.0%)
BACK PAIN	12 (1.6%)	10 (1.5%)	3 (1.1%)	1 (0.4%)
CHEST WALL PAIN	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
FIBROMYALGIA	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
FLANK PAIN	3 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
JOINT SWELLING	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
LIMB DISCOMFORT	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MUSCLE CRAMP	5 (0.6%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
MUSCLE SPASMS	2 (0.3%)	1 (0.1%)	0 (0.0%)	1 (0.4%)
MUSCULAR WEAKNESS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MUSCULOSKELETAL STIFFNESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
MYALGIA	6 (0.8%)	1 (0.1%)	1 (0.4%)	0 (0.0%)
MYOSITIS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PAIN IN EXTREMITY	6 (0.8%)	3 (0.4%)	2 (0.7%)	1 (0.4%)
SENSATION OF HEAVINESS	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
TENDONITIS	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.1%)	3 (0.4%)	0 (0.0%)	0 (0.0%)
CYST	0 (0.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
UTERINE LEIOMYOMA	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)

Note: All Post-partum and HUB Studies: VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-6011.
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Table 5.2.1.1AC
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(All Post-Partum and HUB Studies)
Safety Population

	FCM (N= 773)	Oral Iron (N= 668)	Crossover Study FCM (N= 279)	Crossover Study Placebo (N= 263)
NERVOUS SYSTEM DISORDERS	110 (14.2%)	84 (12.6%)	22 (7.9%)	12 (4.6%)
AMNESIA	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
DIZZINESS	20 (2.6%)	15 (2.2%)	4 (1.4%)	1 (0.4%)
DYSGEUSIA	9 (1.2%)	3 (0.4%)	2 (0.7%)	1 (0.4%)
HEADACHE	77 (10.0%)	61 (9.1%)	14 (5.0%)	8 (3.0%)
HYPOAESTHESIA	1 (0.1%)	0 (0.0%)	0 (0.0%)	2 (0.8%)
LETHARGY	2 (0.3%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
MIGRAINE	2 (0.3%)	6 (0.9%)	1 (0.4%)	0 (0.0%)
NEURALGIA	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PARAESTHESIA	1 (0.1%)	0 (0.0%)	3 (1.1%)	0 (0.0%)
SCIATICA	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SINUS HEADACHE	2 (0.3%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
SOMNOLENCE	2 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
SYNCOPE	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TENSION HEADACHE	2 (0.3%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
TRANSIENT ISCHAEMIC ATTACK	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	4 (0.5%)	4 (0.6%)	0 (0.0%)	0 (0.0%)
LACTATION DISORDER	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MASTITIS POSTPARTUM	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
PERINEAL HAEMATOMA	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
PERIPARTUM CARDIOMYOPATHY	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SUPPRESSED LACTATION	1 (0.1%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
PSYCHIATRIC DISORDERS	17 (2.2%)	15 (2.2%)	0 (0.0%)	1 (0.4%)

Note: All Post-partum and HUB Studies: VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-6011.
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Safety Population

	FCM (N= 773)	Oral Iron (N= 668)	Crossover Study FCM (N= 279)	Crossover Study Placebo (N= 263)
ANXIETY	3 (0.4%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
BIPOLAR DISORDER	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DEPRESSION	2 (0.3%)	4 (0.6%)	0 (0.0%)	0 (0.0%)
DISORIENTATION	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INSOMNIA	2 (0.3%)	6 (0.9%)	0 (0.0%)	1 (0.4%)
MAJOR DEPRESSION	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
PANIC ATTACK	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
POST-TRAUMATIC STRESS DISORDER	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
POSTPARTUM DEPRESSION	8 (1.0%)	4 (0.6%)	0 (0.0%)	0 (0.0%)
SLEEP DISORDER	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
RENAL AND URINARY DISORDERS	3 (0.4%)	6 (0.9%)	0 (0.0%)	0 (0.0%)
CALCULUS URETERIC	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
DYSURIA	2 (0.3%)	3 (0.4%)	0 (0.0%)	0 (0.0%)
NEPHROLITHIASIS	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
RENAL PAIN	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
URINARY HESITATION	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	27 (3.5%)	27 (4.0%)	1 (0.4%)	0 (0.0%)
BARTHOLIN'S CYST	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
BREAST DISORDER	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
BREAST PAIN	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
BREAST TENDERNESS	1 (0.1%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
CERVICAL DISCHARGE	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
CERVICAL DYSPLASIA	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Safety Population

	FCM (N= 773)	Oral Iron (N= 668)	Crossover Study FCM (N= 279)	Crossover Study Placebo (N= 263)
CERVIX DISORDER	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DYSMENORRHOEA	7 (0.9%)	3 (0.4%)	0 (0.0%)	0 (0.0%)
GENITAL PAIN FEMALE	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
MENORRHAGIA	2 (0.3%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
METRORRHAGIA	3 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
NIPPLE DISORDER	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
OVARIAN CYST	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
PELVIC PAIN	0 (0.0%)	4 (0.6%)	1 (0.4%)	0 (0.0%)
PERINEAL PAIN	0 (0.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
PREMENSTRUAL SYNDROME	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PRURITUS GENITAL	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
UTERINE ENLARGEMENT	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
UTERINE HAEMORRHAGE	4 (0.5%)	4 (0.6%)	0 (0.0%)	0 (0.0%)
UTERINE SPASM	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
VAGINAL HAEMORRHAGE	3 (0.4%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
VULVA CYST	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
VULVOVAGINAL DISCOMFORT	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
VULVOVAGINAL DRYNESS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	19 (2.5%)	15 (2.2%)	2 (0.7%)	2 (0.8%)
ASTHMA	0 (0.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
BRONCHOSPASM	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
COUGH	3 (0.4%)	2 (0.3%)	0 (0.0%)	1 (0.4%)
DRY THROAT	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DYSPNOEA	1 (0.1%)	0 (0.0%)	1 (0.4%)	0 (0.0%)

Note: All Post-partum and HUB Studies: VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-6011.
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Safety Population

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EPISTAXIS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INCREASED UPPER AIRWAY SECRETION	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MAXILLARY SINUSITIS	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
NASAL CONGESTION	3 (0.4%)	3 (0.4%)	0 (0.0%)	0 (0.0%)
PARANASAL SINUS HYPERSECRETION	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
PHARYNGOLARYNGEAL PAIN	5 (0.6%)	3 (0.4%)	0 (0.0%)	1 (0.4%)
PRODUCTIVE COUGH	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PULMONARY EMBOLISM	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
PULMONARY OEDEMA	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
RHINORRHOEA	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SINUS CONGESTION	1 (0.1%)	3 (0.4%)	1 (0.4%)	0 (0.0%)
SNEEZING	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TONSILLAR HYPERTROPHY	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
WHEEZING	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
YAWNING	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	51 (6.6%)	17 (2.5%)	9 (3.2%)	2 (0.8%)
ACNE	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
ACNE CYSTIC	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ALOPECIA	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
DERMATITIS CONTACT	3 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DRY SKIN	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
ERYTHEMA	4 (0.5%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
HYPERHIDROSIS	3 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
IDIOPATHIC URTICARIA	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
NAIL DISCOLOURATION	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: All Post-partum and HUB Studies: VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-6011.
Placebo Controlled, Single-Dose Crossover Study: VIT-5006.
Treatment Emergent Adverse Events for 7 days following the First Dose for Placebo Controlled, Single-Dose Crossover Study: VIT-5006.
Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.

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Table 5.2.1.1AC
Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group
(All Post-Partum and HUB Studies)
Safety Population

	FCM (N= 773)	Oral Iron (N= 668)	Crossover Study FCM (N= 279)	Crossover Study Placebo (N= 263)
NIGHT SWEATS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PRURITUS	7 (0.9%)	2 (0.3%)	2 (0.7%)	0 (0.0%)
PRURITUS GENERALISED	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.4%)
RASH	17 (2.2%)	9 (1.3%)	3 (1.1%)	0 (0.0%)
RASH ERYTHEMATOUS	1 (0.1%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
RASH GENERALISED	0 (0.0%)	0 (0.0%)	2 (0.7%)	0 (0.0%)
RASH MACULAR	3 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
RASH MACULO-PAPULAR	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
RASH PAPULAR	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
RASH PRURITIC	2 (0.3%)	1 (0.1%)	1 (0.4%)	0 (0.0%)
SCAR	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SKIN DISCOLOURATION	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SKIN DISORDER	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SKIN IRRITATION	2 (0.3%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
SKIN REACTION	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SKIN ULCER	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
SKIN WARM	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
URTICARIA	6 (0.8%)	3 (0.4%)	0 (0.0%)	0 (0.0%)
URTICARIA GENERALISED	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SOCIAL CIRCUMSTANCES	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
VICTIM OF ABUSE	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
SURGICAL AND MEDICAL PROCEDURES	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SURGERY	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
VAGINAL HYSTERECTOMY	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: All Post-partum and HUB Studies: VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-6011.
Placebo Controlled, Single-Dose Crossover Study: VIT-5006.
Treatment Emergent Adverse Events for 7 days following the First Dose for Placebo Controlled, Single-Dose Crossover Study: VIT-5006.
Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Luitpold Pharmaceuticals, Inc.
FCM
Revised Label for Postpartum and Heavy Uterine Bleeding

Table 5.2.1.1AC
Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group
(All Post-Partum and HUB Studies)
Safety Population

			Crossover Study	
	FCM (N= 773)	Oral Iron (N= 668)	FCM (N= 279)	Placebo (N= 263)
VASCULAR DISORDERS	16 (2.1%)	10 (1.5%)	1 (0.4%)	0 (0.0%)
FLUSHING	4 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HOT FLUSH	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HYPERAEMIA	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HYPERTENSION	5 (0.6%)	9 (1.3%)	1 (0.4%)	0 (0.0%)
HYPOTENSION	3 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PERIPHERAL COLDNESS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
THROMBOPHLEBITIS	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
VARICOSE VEIN	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: All Post-partum and HUB Studies: VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-6011.
Placebo Controlled, Single-Dose Crossover Study: VIT-5006.
Treatment Emergent Adverse Events for 7 days following the First Dose for Placebo Controlled, Single-Dose Crossover Study: VIT-5006.
Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Luitpold Pharmaceuticals, Inc.
FCM
Revised Integrated Summary of Safety (AC)

Table 5.2.1.2AC
Serious Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group
(All Post-Partum and HUB Studies)
Safety Population

	FCM (N= 773)	Oral Iron (N= 668)	Crossover Study FCM (N= 279)	Crossover Study Placebo (N= 263)
AT LEAST ONE SERIOUS ADVERSE EVENT	13 (1.7%)	11 (1.6%)	0 (0.0%)	0 (0.0%)
CARDIAC DISORDERS	2 (0.3%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
CARDIAC FAILURE	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CARDIAC FAILURE CONGESTIVE	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
MITRAL VALVE PROLAPSE	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GASTROINTESTINAL DISORDERS	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
ABDOMINAL PAIN	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
HAEMORRHOIDS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CHEST PAIN	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PYREXIA	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HEPATOBILIARY DISORDERS	2 (0.3%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
CHOLECYSTITIS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CHOLECYSTITIS ACUTE	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CHOLELITHIASIS	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
INFECTIONS AND INFESTATIONS	6 (0.8%)	3 (0.4%)	0 (0.0%)	0 (0.0%)
APPENDICITIS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ENDOMETRITIS	0 (0.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
ENDOMETRITIS DECIDUAL	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PELVIC ABSCESS	0 (0.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)

Note: All Post-partum and HUB Studies: VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-6011.
Placebo Controlled, Single-Dose Crossover Study: VIT-5006.
Treatment Emergent Adverse Events for 7 days following the First Dose for Placebo Controlled, Single-Dose Crossover Study: VIT-5006.
Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.

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Table 5.2.1.2AC
Serious Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group
(All Post-Partum and HUB Studies)
Safety Population

			Crossover Study	
	FCM (N= 773)	Oral Iron (N= 668)	FCM (N= 279)	Placebo (N= 263)
PELVIC INFLAMMATORY DISEASE	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
POSTOPERATIVE INFECTION	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PYELONEPHRITIS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SEPSIS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
UTERINE LEIOMYOMA	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
NERVOUS SYSTEM DISORDERS	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
TRANSIENT ISCHAEMIC ATTACK	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PERIPARTUM CARDIOMYOPATHY	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PSYCHIATRIC DISORDERS	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
MAJOR DEPRESSION	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	3 (0.4%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
METRORRHAGIA	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
UTERINE HAEMORRHAGE	2 (0.3%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)

Note: All Post-partum and HUB Studies: VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-6011.
Placebo Controlled, Single-Dose Crossover Study: VIT-5006.
Treatment Emergent Adverse Events for 7 days following the First Dose for Placebo Controlled, Single-Dose Crossover Study: VIT-5006.
Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.

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Table 5.2.1.2AC
Serious Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group
(All Post-Partum and HUB Studies)
Safety Population

	FCM (N= 773)	Oral Iron (N= 668)	Crossover Study FCM (N= 279)	Crossover Study Placebo (N= 263)
PULMONARY EMBOLISM	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
PULMONARY OEDEMA	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SURGICAL AND MEDICAL PROCEDURES	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
VAGINAL HYSTERECTOMY	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
VASCULAR DISORDERS	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
THROMBOPHLEBITIS	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)

Note: All Post-partum and HUB Studies: VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-6011.
Placebo Controlled, Single-Dose Crossover Study: VIT-5006.
Treatment Emergent Adverse Events for 7 days following the First Dose for Placebo Controlled, Single-Dose Crossover Study: VIT-5006.
Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.

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Table 5.1.1.3
Treatment-Emergent Adverse Events 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)	P-Value (1)
AT LEAST ONE ADVERSE EVENT	509 (48.2%)	443 (53.1%)	0.0332
BLOOD AND LYMPHATIC SYSTEM DISORDERS	5 (0.5%)	1 (0.1%)	0.2375
LEUKOPENIA	2 (0.2%)	0 (0.0%)	
LYMPHADENOPATHY	1 (0.1%)	0 (0.0%)	
THROMBOCYTHAEMIA	1 (0.1%)	1 (0.1%)	
WHITE BLOOD CELL DISORDER	1 (0.1%)	0 (0.0%)	
CARDIAC DISORDERS	14 (1.3%)	9 (1.1%)	0.6780
ARRHYTHMIA SUPRAVENTRICULAR	0 (0.0%)	1 (0.1%)	
ATRIAL FIBRILLATION	0 (0.0%)	1 (0.1%)	
ATRIOVENTRICULAR BLOCK	0 (0.0%)	1 (0.1%)	
BUNDLE BRANCH BLOCK LEFT	2 (0.2%)	0 (0.0%)	
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%)	
CARDIAC FLUTTER	0 (0.0%)	1 (0.1%)	
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%)	1 (0.1%)	
TACHYCARDIA	4 (0.4%)	1 (0.1%)	
EAR AND LABYRINTH DISORDERS	3 (0.3%)	6 (0.7%)	0.1945
EAR DISORDER	1 (0.1%)	0 (0.0%)	
EAR PAIN	1 (0.1%)	3 (0.4%)	
VERTIGO	1 (0.1%)	3 (0.4%)	

All Calculated Dose/First-Dose 1,000 mg Studies: VIT-IV-CL-008, VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-4004, VIT-6011.

Note: Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.
(1) P-Value calculated using Fisher's Exact Test.

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Table 5.1.1.3
Treatment-Emergent Adverse Events 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)	P-Value (1)
ENDOCRINE DISORDERS	1 (0.1%)	2 (0.2%)	0.5863
GOITRE	0 (0.0%)	1 (0.1%)	
HYPERPARATHYROIDISM	1 (0.1%)	0 (0.0%)	
HYPOTHYROIDISM	0 (0.0%)	1 (0.1%)	
EYE DISORDERS	4 (0.4%)	2 (0.2%)	0.6999
CATARACT	0 (0.0%)	1 (0.1%)	
CONJUNCTIVITIS	1 (0.1%)	1 (0.1%)	
EYE PAIN	1 (0.1%)	0 (0.0%)	
EYE PRURITUS	1 (0.1%)	0 (0.0%)	
LACRIMATION INCREASED	1 (0.1%)	0 (0.0%)	
GASTROINTESTINAL DISORDERS	141 (13.3%)	260 (31.2%)	<.0001
ABDOMINAL DISCOMFORT	0 (0.0%)	1 (0.1%)	
ABDOMINAL DISTENSION	0 (0.0%)	7 (0.8%)	
ABDOMINAL MASS	1 (0.1%)	0 (0.0%)	
ABDOMINAL PAIN	28 (2.6%)	16 (1.9%)	
ABDOMINAL PAIN LOWER	5 (0.5%)	2 (0.2%)	
ABDOMINAL PAIN UPPER	13 (1.2%)	12 (1.4%)	
ABDOMINAL TENDERNESS	0 (0.0%)	1 (0.1%)	
ANAL FISTULA	1 (0.1%)	0 (0.0%)	
APHTHOUS STOMATITIS	0 (0.0%)	1 (0.1%)	
COLITIS ULCERATIVE	11 (1.0%)	9 (1.1%)	
COLONIC HAEMORRHAGE	1 (0.1%)	0 (0.0%)	
COLONIC POLYP	1 (0.1%)	0 (0.0%)	
CONSTIPATION	20 (1.9%)	105 (12.6%)	
CROHN'S DISEASE	5 (0.5%)	1 (0.1%)	
DIARRHOEA	16 (1.5%)	33 (4.0%)	
DRY MOUTH	1 (0.1%)	0 (0.0%)	

All Calculated Dose/First-Dose 1,000 mg Studies: VIT-IV-CL-008, VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-4004, VIT-6011.

Note: Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.
(1) P-Value calculated using Fisher's Exact Test.

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Table 5.1.1.3
Treatment-Emergent Adverse Events 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)	P-Value (1)
DYSPEPSIA	3 (0.3%)	8 (1.0%)	
EPIGASTRIC DISCOMFORT	0 (0.0%)	1 (0.1%)	
ERUCTATION	0 (0.0%)	1 (0.1%)	
FAECES DISCOLOURED	0 (0.0%)	12 (1.4%)	
FAECES HARD	0 (0.0%)	3 (0.4%)	
FLATULENCE	5 (0.5%)	6 (0.7%)	
FOOD POISONING	0 (0.0%)	1 (0.1%)	
FREQUENT BOWEL MOVEMENTS	0 (0.0%)	1 (0.1%)	
GASTRIC ULCER	1 (0.1%)	0 (0.0%)	
GASTRITIS	2 (0.2%)	4 (0.5%)	
GASTROINTESTINAL DISCOMFORT	1 (0.1%)	0 (0.0%)	
GASTROINTESTINAL HAEMORRHAGE	1 (0.1%)	3 (0.4%)	
GASTROINTESTINAL PAIN	0 (0.0%)	3 (0.4%)	
GASTROOESOPHAGEAL REFLUX DISEASE	2 (0.2%)	2 (0.2%)	
HAEMATOCHEZIA	5 (0.5%)	0 (0.0%)	
HAEMORRHOIDS	1 (0.1%)	2 (0.2%)	
HIATUS HERNIA	0 (0.0%)	1 (0.1%)	
INFREQUENT BOWEL MOVEMENTS	0 (0.0%)	1 (0.1%)	
INTESTINAL HAEMORRHAGE	0 (0.0%)	1 (0.1%)	
IRRITABLE BOWEL SYNDROME	1 (0.1%)	0 (0.0%)	
LOOSE STOOLS	1 (0.1%)	5 (0.6%)	
MELAENA	1 (0.1%)	0 (0.0%)	
NAUSEA	23 (2.2%)	62 (7.4%)	
ODYNOPHAGIA	0 (0.0%)	1 (0.1%)	
PANCREATITIS	1 (0.1%)	0 (0.0%)	
PANCREATITIS ACUTE	2 (0.2%)	0 (0.0%)	
RECTAL HAEMORRHAGE	2 (0.2%)	1 (0.1%)	
SMALL INTESTINAL HAEMORRHAGE	1 (0.1%)	0 (0.0%)	
STOMACH DISCOMFORT	1 (0.1%)	5 (0.6%)	

All Calculated Dose/First-Dose 1,000 mg Studies: VIT-IV-CL-008, VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-4004, VIT-6011.

Note: Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.
(1) P-Value calculated using Fisher's Exact Test.

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Table 5.1.1.3
Treatment-Emergent Adverse Events 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)	P-Value (1)
TOOTHACHE	5 (0.5%)	5 (0.6%)	
VOMITING	10 (0.9%)	21 (2.5%)	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	116 (11.0%)	37 (4.4%)	<.0001
APPLICATION SITE ERYTHEMA	1 (0.1%)	0 (0.0%)	
APPLICATION SITE INFLAMMATION	0 (0.0%)	1 (0.1%)	
APPLICATION SITE OEDEMA	0 (0.0%)	1 (0.1%)	
APPLICATION SITE PARAESTHESIA	2 (0.2%)	0 (0.0%)	
ASTHENIA	5 (0.5%)	2 (0.2%)	
BLOODY DISCHARGE	1 (0.1%)	0 (0.0%)	
BODY TEMPERATURE INCREASED	7 (0.7%)	0 (0.0%)	
CHEST DISCOMFORT	1 (0.1%)	0 (0.0%)	
CHEST PAIN	8 (0.8%)	0 (0.0%)	
CHILLS	3 (0.3%)	0 (0.0%)	
FATIGUE	16 (1.5%)	8 (1.0%)	
FEELING COLD	2 (0.2%)	0 (0.0%)	
HYPERTHERMIA	1 (0.1%)	1 (0.1%)	
INFLUENZA LIKE ILLNESS	2 (0.2%)	1 (0.1%)	
INFUSION SITE BRUISING	1 (0.1%)	0 (0.0%)	
INFUSION SITE BURNING	7 (0.7%)	0 (0.0%)	
INFUSION SITE OEDEMA	1 (0.1%)	0 (0.0%)	
INFUSION SITE PAIN	6 (0.6%)	0 (0.0%)	
INFUSION SITE PRURITUS	1 (0.1%)	0 (0.0%)	
INFUSION SITE REACTION	8 (0.8%)	0 (0.0%)	
INFUSION SITE SWELLING	1 (0.1%)	0 (0.0%)	
INFUSION SITE WARMTH	1 (0.1%)	0 (0.0%)	
INJECTION SITE BRUISING	1 (0.1%)	0 (0.0%)	
INJECTION SITE ERYTHEMA	2 (0.2%)	0 (0.0%)	
INJECTION SITE EXTRAVASATION	3 (0.3%)	0 (0.0%)	

All Calculated Dose/First-Dose 1,000 mg Studies: VIT-IV-CL-008, VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-4004, VIT-6011.

Note: Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.
(1) P-Value calculated using Fisher's Exact Test.

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Table 5.1.1.3
Treatment-Emergent Adverse Events 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)	P-Value (1)
INJECTION SITE PARAESTHESIA	1 (0.1%)	0 (0.0%)	
INJECTION SITE REACTION	1 (0.1%)	0 (0.0%)	
LOCAL SWELLING	1 (0.1%)	0 (0.0%)	
MALAISE	0 (0.0%)	1 (0.1%)	
OEDEMA	3 (0.3%)	2 (0.2%)	
OEDEMA PERIPHERAL	16 (1.5%)	7 (0.8%)	
PAIN	7 (0.7%)	3 (0.4%)	
PYREXIA	18 (1.7%)	10 (1.2%)	
RIGORS	4 (0.4%)	2 (0.2%)	
SUPRAPUBIC PAIN	0 (0.0%)	1 (0.1%)	
TENDERNESS	1 (0.1%)	0 (0.0%)	
VENIPUNCTURE SITE HAEMORRHAGE	1 (0.1%)	0 (0.0%)	
HEPATOBILIARY DISORDERS	7 (0.7%)	2 (0.2%)	0.3137
AUTOIMMUNE HEPATITIS	1 (0.1%)	0 (0.0%)	
BILE DUCT STONE	1 (0.1%)	0 (0.0%)	
CHOLANGITIS SCLEROSING	1 (0.1%)	0 (0.0%)	
CHOLECYSTITIS	2 (0.2%)	0 (0.0%)	
CHOLECYSTITIS ACUTE	1 (0.1%)	0 (0.0%)	
CHOLELITHIASIS	2 (0.2%)	2 (0.2%)	
CHRONIC HEPATITIS	1 (0.1%)	0 (0.0%)	
IMMUNE SYSTEM DISORDERS	5 (0.5%)	1 (0.1%)	0.2375
FOOD ALLERGY	2 (0.2%)	0 (0.0%)	
HYPERSENSITIVITY	2 (0.2%)	1 (0.1%)	
SEASONAL ALLERGY	1 (0.1%)	0 (0.0%)	
INFECTIONS AND INFESTATIONS	144 (13.6%)	103 (12.4%)	0.4498
ACUTE TONSILLITIS	1 (0.1%)	0 (0.0%)	

All Calculated Dose/First-Dose 1,000 mg Studies: VIT-IV-CL-008, VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-4004, VIT-6011.

Note: Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.
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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Table 5.1.1.3
Treatment-Emergent Adverse Events 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)	P-Value (1)
APPENDICITIS	1 (0.1%)	0 (0.0%)	
BREAST ABSCESS	1 (0.1%)	0 (0.0%)	
BRONCHIAL INFECTION	1 (0.1%)	0 (0.0%)	
BRONCHITIS	4 (0.4%)	1 (0.1%)	
BRONCHITIS ACUTE	3 (0.3%)	0 (0.0%)	
CANDIDIASIS	1 (0.1%)	0 (0.0%)	
CELLULITIS	2 (0.2%)	0 (0.0%)	
CONDYLOMA ACUMINATUM	1 (0.1%)	0 (0.0%)	
CYSTITIS	3 (0.3%)	1 (0.1%)	
DENTAL CARIES	0 (0.0%)	1 (0.1%)	
EAR INFECTION	0 (0.0%)	1 (0.1%)	
ENDOMETRITIS	1 (0.1%)	2 (0.2%)	
ENDOMETRITIS DECIDUAL	1 (0.1%)	0 (0.0%)	
ENTEROVIRUS INFECTION	1 (0.1%)	1 (0.1%)	
ESCHERICHIA INFECTION	1 (0.1%)	0 (0.0%)	
FUNGAL INFECTION	0 (0.0%)	2 (0.2%)	
GASTROENTERITIS	1 (0.1%)	0 (0.0%)	
GASTROENTERITIS VIRAL	4 (0.4%)	5 (0.6%)	
HELICOBACTER GASTRITIS	0 (0.0%)	1 (0.1%)	
HEPATITIS A	1 (0.1%)	0 (0.0%)	
HERPES SIMPLEX	2 (0.2%)	2 (0.2%)	
INFECTION	0 (0.0%)	2 (0.2%)	
INFLUENZA	12 (1.1%)	6 (0.7%)	
KIDNEY INFECTION	0 (0.0%)	1 (0.1%)	
LABYRINTHITIS	1 (0.1%)	0 (0.0%)	
LARYNGITIS	0 (0.0%)	2 (0.2%)	
LARYNGOTRACHEITIS	1 (0.1%)	0 (0.0%)	
MASTITIS	6 (0.6%)	5 (0.6%)	
MASTOIDITIS	1 (0.1%)	0 (0.0%)	

Ā11 Calculated Dose/First-Dose 1,000 mg Studies: VIT-IV-CL-008, VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-4004, VIT-6011.

Note: Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.
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Table 5.1.1.3
Treatment-Emergent Adverse Events 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)	P-Value (1)
NASOPHARYNGITIS	22 (2.1%)	24 (2.9%)	
ORCHITIS	1 (0.1%)	0 (0.0%)	
OTITIS EXTERNA	1 (0.1%)	0 (0.0%)	
OTITIS MEDIA	0 (0.0%)	2 (0.2%)	
OTITIS MEDIA ACUTE	0 (0.0%)	1 (0.1%)	
PELVIC ABSCESS	0 (0.0%)	2 (0.2%)	
PELVIC INFLAMMATORY DISEASE	1 (0.1%)	0 (0.0%)	
PHARYNGITIS	4 (0.4%)	4 (0.5%)	
PHARYNGITIS STREPTOCOCCAL	3 (0.3%)	1 (0.1%)	
PHARYNGOTONSILLITIS	1 (0.1%)	0 (0.0%)	
PILONIDAL CYST	1 (0.1%)	0 (0.0%)	
PNEUMONIA	2 (0.2%)	0 (0.0%)	
POST PROCEDURAL CELLULITIS	0 (0.0%)	1 (0.1%)	
POSTOPERATIVE INFECTION	2 (0.2%)	2 (0.2%)	
POSTPARTUM SEPSIS	1 (0.1%)	0 (0.0%)	
PYELONEPHRITIS	1 (0.1%)	0 (0.0%)	
RESPIRATORY TRACT INFECTION	4 (0.4%)	1 (0.1%)	
RESPIRATORY TRACT INFECTION VIRAL	0 (0.0%)	1 (0.1%)	
RHINITIS	3 (0.3%)	0 (0.0%)	
SEPSIS	2 (0.2%)	0 (0.0%)	
SINUSITIS	10 (0.9%)	8 (1.0%)	
SKIN CANDIDA	1 (0.1%)	0 (0.0%)	
SKIN INFECTION	1 (0.1%)	0 (0.0%)	
TOOTH ABSCESS	5 (0.5%)	0 (0.0%)	
TOOTH INFECTION	1 (0.1%)	0 (0.0%)	
TRACHEITIS	0 (0.0%)	1 (0.1%)	
UPPER RESPIRATORY TRACT INFECTION	13 (1.2%)	13 (1.6%)	
URINARY TRACT INFECTION	16 (1.5%)	13 (1.6%)	
VAGINAL INFECTION	1 (0.1%)	0 (0.0%)	

All Calculated Dose/First-Dose 1,000 mg Studies: VIT-IV-CL-008, VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-4004, VIT-6011.

Note: Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.
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Table 5.1.1.3
Treatment-Emergent Adverse Events 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)	P-Value (1)
VAGINAL MYCOSIS	1 (0.1%)	0 (0.0%)	
VAGINITIS	2 (0.2%)	0 (0.0%)	
VAGINITIS BACTERIAL	1 (0.1%)	1 (0.1%)	
VIRAL INFECTION	3 (0.3%)	3 (0.4%)	
VIRAL UPPER RESPIRATORY TRACT INFECTION	2 (0.2%)	1 (0.1%)	
VULVOVAGINITIS TRICHOMONAL	0 (0.0%)	2 (0.2%)	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	18 (1.7%)	14 (1.7%)	1.0000
ARTERIOVENOUS FISTULA SITE COMPLICATION	0 (0.0%)	1 (0.1%)	
ARTHROPOD BITE	1 (0.1%)	0 (0.0%)	
ARTHROPOD STING	0 (0.0%)	1 (0.1%)	
BURNS SECOND DEGREE	1 (0.1%)	0 (0.0%)	
CONTUSION	3 (0.3%)	2 (0.2%)	
HEAD INJURY	1 (0.1%)	0 (0.0%)	
INCISION SITE COMPLICATION	3 (0.3%)	1 (0.1%)	
INCISION SITE HAEMORRHAGE	1 (0.1%)	0 (0.0%)	
JOINT INJURY	0 (0.0%)	1 (0.1%)	
JOINT SPRAIN	0 (0.0%)	2 (0.2%)	
MUSCLE STRAIN	2 (0.2%)	2 (0.2%)	
PELVIC FRACTURE	1 (0.1%)	0 (0.0%)	
POLYTRAUMATISM	1 (0.1%)	0 (0.0%)	
POST PROCEDURAL DISCHARGE	0 (0.0%)	1 (0.1%)	
POSTOPERATIVE FEVER	1 (0.1%)	0 (0.0%)	
RIB FRACTURE	0 (0.0%)	1 (0.1%)	
SKIN LACERATION	0 (0.0%)	1 (0.1%)	
SOFT TISSUE INJURY	1 (0.1%)	0 (0.0%)	
STERNAL FRACTURE	0 (0.0%)	1 (0.1%)	
SUNBURN	1 (0.1%)	0 (0.0%)	
THERAPEUTIC AGENT TOXICITY	1 (0.1%)	0 (0.0%)	

All Calculated Dose/First-Dose 1,000 mg Studies: VIT-IV-CL-008, VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-4004, VIT-6011.

Note: Subjects are counted once within System Organ Class and Preferred Term.
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Table 5.1.1.3
Treatment-Emergent Adverse Events 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)	P-Value (1)
THERMAL BURN	0 (0.0%)	1 (0.1%)	
INVESTIGATIONS	74 (7.0%)	31 (3.7%)	0.0023
ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED	1 (0.1%)	0 (0.0%)	
ALANINE AMINOTRANSFERASE	0 (0.0%)	1 (0.1%)	
ALANINE AMINOTRANSFERASE INCREASED	14 (1.3%)	15 (1.8%)	
ASPARTATE AMINOTRANSFERASE	0 (0.0%)	1 (0.1%)	
ASPARTATE AMINOTRANSFERASE INCREASED	7 (0.7%)	10 (1.2%)	
BAND NEUTROPHIL COUNT INCREASED	2 (0.2%)	0 (0.0%)	
BASOPHIL COUNT INCREASED	1 (0.1%)	0 (0.0%)	
BLOOD ALKALINE PHOSPHATASE INCREASED	6 (0.6%)	1 (0.1%)	
BLOOD BILIRUBIN INCREASED	2 (0.2%)	0 (0.0%)	
BLOOD CALCIUM DECREASED	2 (0.2%)	0 (0.0%)	
BLOOD GLUCOSE DECREASED	2 (0.2%)	0 (0.0%)	
BLOOD GLUCOSE INCREASED	0 (0.0%)	2 (0.2%)	
BLOOD LACTATE DEHYDROGENASE INCREASED	5 (0.5%)	1 (0.1%)	
BLOOD PHOSPHORUS DECREASED	26 (2.5%)	0 (0.0%)	
BLOOD POTASSIUM DECREASED	5 (0.5%)	0 (0.0%)	
BLOOD POTASSIUM INCREASED	1 (0.1%)	1 (0.1%)	
BLOOD SODIUM INCREASED	1 (0.1%)	0 (0.0%)	
BLOOD THYROID STIMULATING HORMONE INCREASED	0 (0.0%)	1 (0.1%)	
BLOOD UREA DECREASED	1 (0.1%)	0 (0.0%)	
C-REACTIVE PROTEIN INCREASED	7 (0.7%)	3 (0.4%)	
CARDIAC MURMUR	2 (0.2%)	1 (0.1%)	
CAROTID BRUIT	1 (0.1%)	0 (0.0%)	
ELECTROCARDIOGRAM ABNORMAL	0 (0.0%)	1 (0.1%)	
GAMMA-GLUTAMYLTRANSFERASE	1 (0.1%)	0 (0.0%)	
GAMMA-GLUTAMYLTRANSFERASE ABNORMAL	0 (0.0%)	1 (0.1%)	
GAMMA-GLUTAMYLTRANSFERASE INCREASED	10 (0.9%)	2 (0.2%)	

All Calculated Dose/First-Dose 1,000 mg Studies: VIT-IV-CL-008, VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-4004, VIT-6011.

Note: Subjects are counted once within System Organ Class and Preferred Term.
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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Table 5.1.1.3
Treatment-Emergent Adverse Events 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)	P-Value (1)
HEART RATE INCREASED	2 (0.2%)	1 (0.1%)	
HEART RATE IRREGULAR	1 (0.1%)	1 (0.1%)	
HEPATIC ENZYME INCREASED	2 (0.2%)	2 (0.2%)	
HIGH DENSITY LIPOPROTEIN INCREASED	1 (0.1%)	0 (0.0%)	
LIVER FUNCTION TEST ABNORMAL	2 (0.2%)	1 (0.1%)	
LOW DENSITY LIPOPROTEIN DECREASED	1 (0.1%)	0 (0.0%)	
NEUTROPHIL COUNT ABNORMAL	1 (0.1%)	0 (0.0%)	
NEUTROPHIL COUNT INCREASED	2 (0.2%)	1 (0.1%)	
RED CELL DISTRIBUTION WIDTH INCREASED	1 (0.1%)	0 (0.0%)	
SMEAR CERVIX ABNORMAL	0 (0.0%)	1 (0.1%)	
TRANSAMINASES INCREASED	0 (0.0%)	1 (0.1%)	
URINE ANALYSIS ABNORMAL	0 (0.0%)	1 (0.1%)	
WEIGHT INCREASED	0 (0.0%)	1 (0.1%)	
WHITE BLOOD CELL COUNT INCREASED	3 (0.3%)	1 (0.1%)	
METABOLISM AND NUTRITION DISORDERS	18 (1.7%)	11 (1.3%)	0.5744
ACIDOSIS	1 (0.1%)	0 (0.0%)	
ANOREXIA	1 (0.1%)	2 (0.2%)	
DECREASED APPETITE	0 (0.0%)	3 (0.4%)	
ELECTROLYTE DEPLETION	1 (0.1%)	0 (0.0%)	
FLUID RETENTION	1 (0.1%)	0 (0.0%)	
GOUT	1 (0.1%)	0 (0.0%)	
HYPERCALCAEMIA	1 (0.1%)	0 (0.0%)	
HYPERCHOLESTEROLAEMIA	1 (0.1%)	0 (0.0%)	
HYPERGLYCAEMIA	1 (0.1%)	1 (0.1%)	
HYPERKALAEMIA	6 (0.6%)	1 (0.1%)	
HYPERLIPIDAEMIA	1 (0.1%)	2 (0.2%)	
HYPERPHOSPHATAEMIA	0 (0.0%)	1 (0.1%)	
HYPOGLYCAEMIA	2 (0.2%)	1 (0.1%)	

All Calculated Dose/First-Dose 1,000 mg Studies: VIT-IV-CL-008, VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-4004, VIT-6011.

Note: Subjects are counted once within System Organ Class and Preferred Term.
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(1) P-Value calculated using Fisher's Exact Test.

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Table 5.1.1.3
Treatment-Emergent Adverse Events 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)	P-Value (1)
HYPOKALAEMIA	2 (0.2%)	0 (0.0%)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	58 (5.5%)	31 (3.7%)	0.0801
ARTHRALGIA	15 (1.4%)	8 (1.0%)	
ARTHRITIS	1 (0.1%)	0 (0.0%)	
ARTHRITIS REACTIVE	0 (0.0%)	1 (0.1%)	
BACK PAIN	17 (1.6%)	11 (1.3%)	
BURSITIS	1 (0.1%)	0 (0.0%)	
CHEST WALL PAIN	0 (0.0%)	1 (0.1%)	
FIBROMYALGIA	0 (0.0%)	1 (0.1%)	
FLANK PAIN	3 (0.3%)	0 (0.0%)	
GROIN PAIN	1 (0.1%)	0 (0.0%)	
JOINT SWELLING	2 (0.2%)	0 (0.0%)	
LIMB DISCOMFORT	1 (0.1%)	0 (0.0%)	
MUSCLE CRAMP	6 (0.6%)	2 (0.2%)	
MUSCLE SPASMS	2 (0.2%)	1 (0.1%)	
MUSCULAR WEAKNESS	1 (0.1%)	0 (0.0%)	
MYALGIA	12 (1.1%)	1 (0.1%)	
MYOSITIS	1 (0.1%)	0 (0.0%)	
PAIN IN EXTREMITY	6 (0.6%)	4 (0.5%)	
SENSATION OF HEAVINESS	0 (0.0%)	1 (0.1%)	
TENDONITIS	3 (0.3%)	0 (0.0%)	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	4 (0.4%)	3 (0.4%)	1.0000
COLON CANCER	1 (0.1%)	0 (0.0%)	
CYST	0 (0.0%)	2 (0.2%)	
OVARIAN CANCER	1 (0.1%)	0 (0.0%)	
RECTAL CANCER	1 (0.1%)	0 (0.0%)	

All Calculated Dose/First-Dose 1,000 mg Studies: VIT-IV-CL-008, VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-4004, VIT-6011.

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Table 5.1.1.3
Treatment-Emergent Adverse Events 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)	P-Value (1)
UTERINE LEIOMYOMA	1 (0.1%)	1 (0.1%)	
NERVOUS SYSTEM DISORDERS	125 (11.8%)	92 (11.0%)	0.6115
AMNESIA	0 (0.0%)	1 (0.1%)	
CEREBROVASCULAR ACCIDENT	0 (0.0%)	1 (0.1%)	
DIZZINESS	23 (2.2%)	17 (2.0%)	
DYSGEUSIA	11 (1.0%)	3 (0.4%)	
HEADACHE	88 (8.3%)	64 (7.7%)	
HYPOAESTHESIA	1 (0.1%)	1 (0.1%)	
LETHARGY	2 (0.2%)	1 (0.1%)	
MIGRAINE	2 (0.2%)	6 (0.7%)	
NEURALGIA	1 (0.1%)	0 (0.0%)	
NEUROPATHY	1 (0.1%)	0 (0.0%)	
PARAESTHESIA	1 (0.1%)	1 (0.1%)	
SCIATICA	1 (0.1%)	0 (0.0%)	
SINUS HEADACHE	2 (0.2%)	1 (0.1%)	
SOMNOLENCE	2 (0.2%)	0 (0.0%)	
SYNCOPE	2 (0.2%)	0 (0.0%)	
TENSION HEADACHE	2 (0.2%)	2 (0.2%)	
TRANSIENT ISCHAEMIC ATTACK	0 (0.0%)	1 (0.1%)	
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	4 (0.4%)	4 (0.5%)	0.7374
LACTATION DISORDER	2 (0.2%)	0 (0.0%)	
MASTITIS POSTPARTUM	0 (0.0%)	1 (0.1%)	
PERINEAL HAEMATOMA	0 (0.0%)	1 (0.1%)	
PERIPARTUM CARDIOMYOPATHY	1 (0.1%)	0 (0.0%)	
SUPPRESSED LACTATION	1 (0.1%)	2 (0.2%)	
PSYCHIATRIC DISORDERS	17 (1.6%)	15 (1.8%)	0.8579

All Calculated Dose/First-Dose 1,000 mg Studies: VIT-IV-CL-008, VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-4004, VIT-6011.

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Table 5.1.1.3
Treatment-Emergent Adverse Events 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)	P-Value (1)
ANXIETY	3 (0.3%)	2 (0.2%)	
BIPOLAR DISORDER	1 (0.1%)	0 (0.0%)	
DEPRESSION	2 (0.2%)	4 (0.5%)	
DISORIENTATION	1 (0.1%)	0 (0.0%)	
INSOMNIA	2 (0.2%)	6 (0.7%)	
MAJOR DEPRESSION	0 (0.0%)	1 (0.1%)	
PANIC ATTACK	1 (0.1%)	0 (0.0%)	
POST-TRAUMATIC STRESS DISORDER	1 (0.1%)	0 (0.0%)	
POSTPARTUM DEPRESSION	8 (0.8%)	4 (0.5%)	
SLEEP DISORDER	1 (0.1%)	0 (0.0%)	
RENAL AND URINARY DISORDERS	6 (0.6%)	9 (1.1%)	0.2966
CALCULUS URETERIC	0 (0.0%)	1 (0.1%)	
DYSURIA	2 (0.2%)	3 (0.4%)	
GLOMERULONEPHRITIS PROLIFERATIVE	0 (0.0%)	1 (0.1%)	
HAEMATURIA	2 (0.2%)	0 (0.0%)	
NEPHROLITHIASIS	0 (0.0%)	1 (0.1%)	
RENAL FAILURE CHRONIC	1 (0.1%)	2 (0.2%)	
RENAL PAIN	1 (0.1%)	0 (0.0%)	
URINARY HESITATION	0 (0.0%)	1 (0.1%)	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	29 (2.7%)	27 (3.2%)	0.5854
BARTHOLIN'S CYST	1 (0.1%)	0 (0.0%)	
BREAST DISORDER	1 (0.1%)	0 (0.0%)	
BREAST PAIN	2 (0.2%)	0 (0.0%)	
BREAST TENDERNESS	1 (0.1%)	2 (0.2%)	
CERVICAL DISCHARGE	0 (0.0%)	1 (0.1%)	
CERVICAL DYSPLASIA	1 (0.1%)	0 (0.0%)	
CERVIX DISORDER	1 (0.1%)	0 (0.0%)	

All Calculated Dose/First-Dose 1,000 mg Studies: VIT-IV-CL-008, VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-4004, VIT-6011.

Note: Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.
(1) P-Value calculated using Fisher's Exact Test.

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Table 5.1.1.3
Treatment-Emergent Adverse Events 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)	P-Value (1)
DYSMENORRHOEA	7 (0.7%)	3 (0.4%)	
GENITAL PAIN FEMALE	0 (0.0%)	1 (0.1%)	
GENITAL PRURITUS FEMALE	1 (0.1%)	0 (0.0%)	
MENORRHAGIA	2 (0.2%)	2 (0.2%)	
METRORRHAGIA	3 (0.3%)	0 (0.0%)	
NIPPLE DISORDER	0 (0.0%)	1 (0.1%)	
OVARIAN CYST	0 (0.0%)	1 (0.1%)	
PELVIC PAIN	0 (0.0%)	4 (0.5%)	
PERINEAL PAIN	0 (0.0%)	2 (0.2%)	
PREMENSTRUAL SYNDROME	1 (0.1%)	0 (0.0%)	
PRURITUS GENITAL	1 (0.1%)	0 (0.0%)	
UTERINE ENLARGEMENT	0 (0.0%)	1 (0.1%)	
UTERINE HAEMORRHAGE	4 (0.4%)	4 (0.5%)	
UTERINE SPASM	0 (0.0%)	1 (0.1%)	
VAGINAL DISCHARGE	1 (0.1%)	0 (0.0%)	
VAGINAL HAEMORRHAGE	3 (0.3%)	2 (0.2%)	
VULVA CYST	0 (0.0%)	1 (0.1%)	
VULVOVAGINAL DISCOMFORT	0 (0.0%)	1 (0.1%)	
VULVOVAGINAL DRYNESS	1 (0.1%)	0 (0.0%)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	23 (2.2%)	21 (2.5%)	0.6473
ASTHMA	0 (0.0%)	3 (0.4%)	
BRONCHOSPASM	0 (0.0%)	1 (0.1%)	
COUGH	3 (0.3%)	3 (0.4%)	
DRY THROAT	1 (0.1%)	0 (0.0%)	
DYSPNOEA	2 (0.2%)	2 (0.2%)	
DYSPNOEA EXACERBATED	1 (0.1%)	0 (0.0%)	
EPISTAXIS	2 (0.2%)	1 (0.1%)	
INCREASED UPPER AIRWAY SECRETION	1 (0.1%)	0 (0.0%)	

All Calculated Dose/First-Dose 1,000 mg Studies: VIT-IV-CL-008, VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-4004, VIT-6011.

Note: Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.
(1) P-Value calculated using Fisher's Exact Test.

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Table 5.1.1.3
Treatment-Emergent Adverse Events 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)	P-Value (1)
MAXILLARY SINUSITIS	0 (0.0%)	1 (0.1%)	
NASAL CONGESTION	3 (0.3%)	4 (0.5%)	
PARANASAL SINUS HYPERSECRETION	1 (0.1%)	1 (0.1%)	
PHARYNGOLARYNGEAL PAIN	5 (0.5%)	3 (0.4%)	
PRODUCTIVE COUGH	1 (0.1%)	0 (0.0%)	
PULMONARY EMBOLISM	1 (0.1%)	1 (0.1%)	
PULMONARY OEDEMA	1 (0.1%)	0 (0.0%)	
RHINORRHOEA	2 (0.2%)	0 (0.0%)	
SINUS CONGESTION	1 (0.1%)	3 (0.4%)	
SNEEZING	1 (0.1%)	0 (0.0%)	
TONSILLAR HYPERTROPHY	0 (0.0%)	1 (0.1%)	
WHEEZING	1 (0.1%)	0 (0.0%)	
YAWNING	1 (0.1%)	0 (0.0%)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	70 (6.6%)	20 (2.4%)	<.0001
ACNE	0 (0.0%)	1 (0.1%)	
ACNE CYSTIC	1 (0.1%)	0 (0.0%)	
ALOPECIA	1 (0.1%)	1 (0.1%)	
DERMATITIS CONTACT	3 (0.3%)	0 (0.0%)	
DRY SKIN	0 (0.0%)	1 (0.1%)	
ERYTHEMA	4 (0.4%)	1 (0.1%)	
HYPERHIDROSIS	4 (0.4%)	0 (0.0%)	
IDIOPATHIC URTICARIA	1 (0.1%)	0 (0.0%)	
LEUKOCYTOCLASTIC VASCULITIS	1 (0.1%)	0 (0.0%)	
NAIL DISCOLOURATION	1 (0.1%)	0 (0.0%)	
NIGHT SWEATS	2 (0.2%)	0 (0.0%)	
PRURITUS	9 (0.9%)	2 (0.2%)	
PRURITUS GENERALISED	0 (0.0%)	1 (0.1%)	
PURPURA SENILE	1 (0.1%)	0 (0.0%)	

All Calculated Dose/First-Dose 1,000 mg Studies: VIT-IV-CL-008, VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-4004, VIT-6011.

Note: Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.
(1) P-Value calculated using Fisher's Exact Test.

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Table 5.1.1.3
Treatment-Emergent Adverse Events 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)	P-Value (1)
RASH	22 (2.1%)	10 (1.2%)	
RASH ERYTHEMATOUS	3 (0.3%)	0 (0.0%)	
RASH MACULAR	3 (0.3%)	0 (0.0%)	
RASH MACULO-PAPULAR	1 (0.1%)	0 (0.0%)	
RASH PRURITIC	2 (0.2%)	1 (0.1%)	
SCAR	2 (0.2%)	0 (0.0%)	
SKIN DISCOLOURATION	3 (0.3%)	0 (0.0%)	
SKIN DISORDER	1 (0.1%)	0 (0.0%)	
SKIN IRRITATION	2 (0.2%)	1 (0.1%)	
SKIN LESION	0 (0.0%)	1 (0.1%)	
SKIN REACTION	1 (0.1%)	0 (0.0%)	
SKIN ULCER	3 (0.3%)	0 (0.0%)	
SKIN WARM	1 (0.1%)	0 (0.0%)	
URTICARIA	9 (0.9%)	3 (0.4%)	
URTICARIA GENERALISED	1 (0.1%)	0 (0.0%)	
SOCIAL CIRCUMSTANCES	0 (0.0%)	1 (0.1%)	0.4410
VICTIM OF ABUSE	0 (0.0%)	1 (0.1%)	
SURGICAL AND MEDICAL PROCEDURES	2 (0.2%)	0 (0.0%)	0.5067
SURGERY	1 (0.1%)	0 (0.0%)	
VAGINAL HYSTERECTOMY	1 (0.1%)	0 (0.0%)	
VASCULAR DISORDERS	27 (2.6%)	13 (1.6%)	0.1495
FLUSHING	4 (0.4%)	1 (0.1%)	
HAEMATOMA	1 (0.1%)	0 (0.0%)	
HOT FLUSH	2 (0.2%)	1 (0.1%)	
HYPERAEMIA	1 (0.1%)	0 (0.0%)	
HYPERTENSION	7 (0.7%)	11 (1.3%)	

All Calculated Dose/First-Dose 1,000 mg Studies: VIT-IV-CL-008, VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-4004, VIT-6011.

Note: Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.
(1) P-Value calculated using Fisher's Exact Test.

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Table 5.1.1.3
Treatment-Emergent Adverse Events 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)	P-Value (1)
HYPOTENSION	8 (0.8%)	0 (0.0%)	
JUGULAR VEIN DISTENSION	1 (0.1%)	0 (0.0%)	
PERIPHERAL COLDNESS	1 (0.1%)	0 (0.0%)	
PHLEBITIS	1 (0.1%)	0 (0.0%)	
POOR VENOUS ACCESS	1 (0.1%)	0 (0.0%)	
THROMBOPHLEBITIS	0 (0.0%)	1 (0.1%)	
VARICOSE VEIN	1 (0.1%)	0 (0.0%)	

All Calculated Dose/First-Dose 1,000 mg Studies: VIT-IV-CL-008, VIT-IV-CL-009, VIT-3001, VIT-4002, VIT-4003, VIT-4004, VIT-6011.

Note: Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.
(1) P-Value calculated using Fisher's Exact Test.

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Luitpold Pharmaceuticals, Inc.
FCM
Revised Integrated Summary of Safety

Table 8.3
Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and FCM Courses Received
(VIT-4004 and VIT-5005 Studies)
Safety Population

	FCM (N = 199)					
	>= 1 Course (N=199)	>= 2 Courses (N=134)	>= 3 Courses (N=85)	>= 4 Courses (N=55)	>= 5 Courses (N=25)	>= 6 Courses (N=14)
AT LEAST ONE ADVERSE EVENT	74 (37.2%)	54 (40.3%)	34 (40.0%)	22 (40.0%)	11 (44.0%)	6 (42.9%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PANCYTOPENIA	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CARDIAC DISORDERS	8 (4.0%)	4 (3.0%)	3 (3.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ACUTE MYOCARDIAL INFARCTION	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ANGINA PECTORIS	1 (0.5%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ANGINA UNSTABLE	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
BRADYCARDIA	1 (0.5%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CARDIAC FAILURE CONGESTIVE	2 (1.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CARDIAC FLUTTER	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CORONARY ARTERY DISEASE	2 (1.0%)	1 (0.7%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MYOCARDIAL INFARCTION	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PALPITATIONS	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
EAR AND LABYRINTH DISORDERS	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (1.8%)	1 (4.0%)	0 (0.0%)
DEAFNESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
EAR PAIN	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
EAR PRURITUS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)
ENDOCRINE DISORDERS	1 (0.5%)	1 (0.7%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HYPERPARATHYROIDISM	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HYPERPARATHYROIDISM SECONDARY	0 (0.0%)	1 (0.7%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: All doses received in a 21 day period is a course. All AEs that occurred from the start date of a course to the start date of the next course assigned to that course. AEs occurring after the end of the last course are included in the last course. All AEs occurring from the beginning of course 6 are included in the >= 6 Courses column.

Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.

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Luitpold Pharmaceuticals, Inc.
FCM
Revised Integrated Summary of Safety

Table 8.3
Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and FCM Courses Received
(VIT-4004 and VIT-5005 Studies)
Safety Population

	FCM (N = 199)					
	>= 1 Course (N=199)	>= 2 Courses (N=134)	>= 3 Courses (N=85)	>= 4 Courses (N=55)	>= 5 Courses (N=25)	>= 6 Courses (N=14)
EYE DISORDERS	5 (2.5%)	2 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CONJUNCTIVITIS	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DIABETIC RETINOPATHY	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
EYE PAIN	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
EYE PRURITUS	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PHOTOPSIA	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
RETINAL DETACHMENT	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
VISION BLURRED	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GASTROINTESTINAL DISORDERS	13 (6.5%)	6 (4.5%)	5 (5.9%)	6 (10.9%)	4 (16.0%)	0 (0.0%)
ABDOMINAL DISTENSION	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)
ABDOMINAL PAIN	1 (0.5%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ABDOMINAL PAIN UPPER	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
COLONIC POLYP	1 (0.5%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CONSTIPATION	3 (1.5%)	0 (0.0%)	1 (1.2%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
DIARRHOEA	2 (1.0%)	1 (0.7%)	1 (1.2%)	3 (5.5%)	1 (4.0%)	0 (0.0%)
DYSPEPSIA	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GASTROINTESTINAL HAEMORRHAGE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)
GASTROOESOPHAGEAL REFLUX DISEASE	1 (0.5%)	1 (0.7%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
HIATUS HERNIA	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
LARGE INTESTINE PERFORATION	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MELAENA	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
NAUSEA	2 (1.0%)	1 (0.7%)	3 (3.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PANCREATITIS	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PANCREATITIS ACUTE	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: All doses received in a 21 day period is a course. All AEs that occurred from the start date of a course to the start date of the next course assigned to that course. AEs occurring after the end of the last course are included in the last course. All AEs occurring from the beginning of course 6 are included in the >= 6 Courses column.

Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.

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Table 8.3
Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and FCM Courses Received
(VIT-4004 and VIT-5005 Studies)
Safety Population

	FCM (N = 199)					
	>= 1 Course (N=199)	>= 2 Courses (N=134)	>= 3 Courses (N=85)	>= 4 Courses (N=55)	>= 5 Courses (N=25)	>= 6 Courses (N=14)
RECTAL HAEMORRHAGE	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
UMBILICAL HERNIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)
VOMITING	1 (0.5%)	1 (0.7%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	20 (10.1%)	11 (8.2%)	6 (7.1%)	8 (14.5%)	5 (20.0%)	0 (0.0%)
ASTHENIA	0 (0.0%)	1 (0.7%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CHEST DISCOMFORT	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CHEST PAIN	1 (0.5%)	2 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
FATIGUE	2 (1.0%)	1 (0.7%)	0 (0.0%)	2 (3.6%)	1 (4.0%)	0 (0.0%)
FEELING ABNORMAL	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
FEELING COLD	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INFLUENZA LIKE ILLNESS	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INFUSION SITE PAIN	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
INFUSION SITE REACTION	3 (1.5%)	1 (0.7%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INJECTION SITE DISCOLOURATION	0 (0.0%)	1 (0.7%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INJECTION SITE HAEMORRHAGE	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
LOWER EXTREMITY MASS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
MALAISE	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
OEDEMA	1 (0.5%)	1 (0.7%)	0 (0.0%)	2 (3.6%)	2 (8.0%)	0 (0.0%)
OEDEMA PERIPHERAL	9 (4.5%)	2 (1.5%)	3 (3.5%)	2 (3.6%)	2 (8.0%)	0 (0.0%)
RIGORS	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TENDERNESS	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
IMMUNE SYSTEM DISORDERS	2 (1.0%)	0 (0.0%)	1 (1.2%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
DRUG HYPERSENSITIVITY	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: All doses received in a 21 day period is a course. All AEs that occurred from the start date of a course to the start date of the next course assigned to that course. AEs occurring after the end of the last course are included in the last course. All AEs occurring from the beginning of course 6 are included in the >= 6 Courses column.

Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.

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Revised Integrated Summary of Safety

Table 8.3
Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and FCM Courses Received
(VIT-4004 and VIT-5005 Studies)
Safety Population

	FCM (N = 199)					
	>= 1 Course (N=199)	>= 2 Courses (N=134)	>= 3 Courses (N=85)	>= 4 Courses (N=55)	>= 5 Courses (N=25)	>= 6 Courses (N=14)
SEASONAL ALLERGY	2 (1.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
INFECTIONS AND INFESTATIONS	20 (10.1%)	18 (13.4%)	7 (8.2%)	5 (9.1%)	2 (8.0%)	2 (14.3%)
ABSCESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)
BRONCHITIS	2 (1.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CELLULITIS	0 (0.0%)	2 (1.5%)	2 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DENTAL CARIES	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DIVERTICULITIS	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
FURUNCLE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)
GASTROENTERITIS	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GASTROINTESTINAL INFECTION	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HERPES SIMPLEX	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INFLUENZA	1 (0.5%)	0 (0.0%)	1 (1.2%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
LOCALISED INFECTION	0 (0.0%)	1 (0.7%)	1 (1.2%)	2 (3.6%)	0 (0.0%)	0 (0.0%)
MASTOIDITIS	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
NASOPHARYNGITIS	1 (0.5%)	4 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PERTUSSIS	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PYELONEPHRITIS	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
RESPIRATORY TRACT INFECTION	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
RHINITIS	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SEPSIS	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SINUSITIS	0 (0.0%)	2 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SKIN INFECTION	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TINEA INFECTION	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TOOTH ABSCESS	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: All doses received in a 21 day period is a course. All AEs that occurred from the start date of a course to the start date of the next course assigned to that course. AEs occurring after the end of the last course are included in the last course. All AEs occurring from the beginning of course 6 are included in the >= 6 Courses column.

Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Luitpold Pharmaceuticals, Inc.
FCM
Revised Integrated Summary of Safety

Table 8.3
Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and FCM Courses Received
(VIT-4004 and VIT-5005 Studies)
Safety Population

	FCM (N = 199)					
	>= 1 Course (N=199)	>= 2 Courses (N=134)	>= 3 Courses (N=85)	>= 4 Courses (N=55)	>= 5 Courses (N=25)	>= 6 Courses (N=14)
UPPER RESPIRATORY TRACT INFECTION	4 (2.0%)	0 (0.0%)	1 (1.2%)	1 (1.8%)	0 (0.0%)	1 (7.1%)
URINARY TRACT INFECTION	5 (2.5%)	4 (3.0%)	2 (2.4%)	1 (1.8%)	0 (0.0%)	1 (7.1%)
VIRAL UPPER RESPIRATORY TRACT INFECTION	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
WOUND INFECTION	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	5 (2.5%)	10 (7.5%)	1 (1.2%)	3 (5.5%)	1 (4.0%)	1 (7.1%)
BITE	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CONTUSION	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
EXCORIATION	0 (0.0%)	2 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
FEMUR FRACTURE	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
FIBULA FRACTURE	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
FOOT FRACTURE	1 (0.5%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
FRACTURED COCCYX	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
JOINT INJURY	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MUSCLE STRAIN	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PAIN TRAUMA ACTIVATED	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PELVIC FRACTURE	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
POLYTRAUMATISM	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
POSTOPERATIVE FEVER	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SCRATCH	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
SKIN LACERATION	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
SOFT TISSUE INJURY	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
STRESS FRACTURE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
THERAPEUTIC AGENT TOXICITY	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
UPPER LIMB FRACTURE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)

Note: All doses received in a 21 day period is a course. All AEs that occurred from the start date of a course to the start date of the next course assigned to that course. AEs occurring after the end of the last course are included in the last course. All AEs occurring from the beginning of course 6 are included in the >= 6 Courses column.

Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Luitpold Pharmaceuticals, Inc.
FCM
Revised Integrated Summary of Safety

Table 8.3
Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and FCM Courses Received
(VIT-4004 and VIT-5005 Studies)
Safety Population

	FCM (N = 199)					
	>= 1 Course (N=199)	>= 2 Courses (N=134)	>= 3 Courses (N=85)	>= 4 Courses (N=55)	>= 5 Courses (N=25)	>= 6 Courses (N=14)
VASCULAR INJURY	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INVESTIGATIONS	2 (1.0%)	3 (2.2%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
CARDIAC MURMUR	1 (0.5%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CAROTID BRUIT	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HEART RATE IRREGULAR	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PULSE ABNORMAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
WEIGHT INCREASED	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
METABOLISM AND NUTRITION DISORDERS	12 (6.0%)	6 (4.5%)	6 (7.1%)	1 (1.8%)	1 (4.0%)	1 (7.1%)
ACIDOSIS	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ANOREXIA	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
FLUID RETENTION	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GOUT	1 (0.5%)	1 (0.7%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HYPERCHOLESTEROLAEMIA	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HYPERGLYCAEMIA	0 (0.0%)	1 (0.7%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HYPERKALAEMIA	4 (2.0%)	2 (1.5%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HYPERLIPIDAEMIA	1 (0.5%)	0 (0.0%)	2 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HYPERPHOSPHATAEMIA	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
HYPOGLYCAEMIA	2 (1.0%)	2 (1.5%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HYPOKALAEMIA	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
METABOLIC ACIDOSIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)
VITAMIN D DEFICIENCY	1 (0.5%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	8 (4.0%)	7 (5.2%)	9 (10.6%)	1 (1.8%)	1 (4.0%)	0 (0.0%)

Note: All doses received in a 21 day period is a course. All AEs that occurred from the start date of a course to the start date of the next course assigned to that course. AEs occurring after the end of the last course are included in the last course. All AEs occurring from the beginning of course 6 are included in the >= 6 Courses column.

Subjects are counted once within System Organ Class and Preferred Term.
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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Table 8.3
Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and FCM Courses Received
(VIT-4004 and VIT-5005 Studies)
Safety Population

	FCM (N = 199)					
	>= 1 Course (N=199)	>= 2 Courses (N=134)	>= 3 Courses (N=85)	>= 4 Courses (N=55)	>= 5 Courses (N=25)	>= 6 Courses (N=14)
ARTHRALGIA	2 (1.0%)	4 (3.0%)	2 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
BACK PAIN	1 (0.5%)	0 (0.0%)	2 (2.4%)	0 (0.0%)	1 (4.0%)	0 (0.0%)
BURSITIS	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GROIN PAIN	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
JOINT SWELLING	0 (0.0%)	1 (0.7%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
LOCALISED OSTEOARTHRITIS	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MUSCLE CRAMP	1 (0.5%)	0 (0.0%)	2 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MYALGIA	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
OSTEOARTHRITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
PAIN IN EXTREMITY	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
RENAL OSTEODYSTROPHY	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SPONDYLITIS	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SYNOVITIS	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	2 (1.0%)	1 (0.7%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
BASAL CELL CARCINOMA	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
COLON CANCER	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MYELODYSPLASTIC SYNDROME	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
OVARIAN CANCER	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
NERVOUS SYSTEM DISORDERS	8 (4.0%)	5 (3.7%)	5 (5.9%)	4 (7.3%)	0 (0.0%)	0 (0.0%)
ANOXIC ENCEPHALOPATHY	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
CAROTID ARTERY DISEASE	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DIZZINESS	2 (1.0%)	1 (0.7%)	2 (2.4%)	1 (1.8%)	0 (0.0%)	0 (0.0%)

Note: All doses received in a 21 day period is a course. All AEs that occurred from the start date of a course to the start date of the next course assigned to that course. AEs occurring after the end of the last course are included in the last course. All AEs occurring from the beginning of course 6 are included in the >= 6 Courses column.

Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.

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Table 8.3
Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and FCM Courses Received
(VIT-4004 and VIT-5005 Studies)
Safety Population

	FCM (N = 199)					
	>= 1 Course (N=199)	>= 2 Courses (N=134)	>= 3 Courses (N=85)	>= 4 Courses (N=55)	>= 5 Courses (N=25)	>= 6 Courses (N=14)
DYSGEUSIA	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HEADACHE	4 (2.0%)	1 (0.7%)	1 (1.2%)	2 (3.6%)	0 (0.0%)	0 (0.0%)
LETHARGY	0 (0.0%)	1 (0.7%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MEMORY IMPAIRMENT	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
NEUROPATHY	1 (0.5%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PARAESTHESIA ORAL	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SLEEP APNOEA SYNDROME	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PSYCHIATRIC DISORDERS	0 (0.0%)	1 (0.7%)	1 (1.2%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
DEPRESSION	0 (0.0%)	1 (0.7%)	1 (1.2%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
RENAL AND URINARY DISORDERS	2 (1.0%)	0 (0.0%)	2 (2.4%)	0 (0.0%)	1 (4.0%)	1 (7.1%)
AZOTAEMIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	1 (7.1%)
BLADDER DISORDER	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HAEMATURIA	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
RENAL FAILURE CHRONIC	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
URINARY RETENTION	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
URINARY TRACT OBSTRUCTION	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.5%)	1 (0.7%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
BREAST PAIN	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GENITAL PRURITUS FEMALE	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MENORRHAGIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
VAGINAL DISCHARGE	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: All doses received in a 21 day period is a course. All AEs that occurred from the start date of a course to the start date of the next course assigned to that course. AEs occurring after the end of the last course are included in the last course. All AEs occurring from the beginning of course 6 are included in the >= 6 Courses column.

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Table 8.3
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Safety Population

	FCM (N = 199)					
	>= 1 Course (N=199)	>= 2 Courses (N=134)	>= 3 Courses (N=85)	>= 4 Courses (N=55)	>= 5 Courses (N=25)	>= 6 Courses (N=14)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4 (2.0%)	7 (5.2%)	7 (8.2%)	6 (10.9%)	0 (0.0%)	1 (7.1%)
ABNORMAL CHEST SOUND	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ASTHMA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
BRONCHOSPASM	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
COUGH	1 (0.5%)	2 (1.5%)	2 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DYSPNOEA	2 (1.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DYSPNOEA EXACERBATED	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
EPISTAXIS	0 (0.0%)	3 (2.2%)	1 (1.2%)	1 (1.8%)	0 (0.0%)	1 (7.1%)
NASAL CONGESTION	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PHARYNGOLARYNGEAL PAIN	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PULMONARY EMBOLISM	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PULMONARY OEDEMA	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
RALES	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
RESPIRATORY DISTRESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
RESPIRATORY TRACT CONGESTION	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
RHINORRHOEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
SINUS CONGESTION	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
WHEEZING	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	5 (2.5%)	8 (6.0%)	9 (10.6%)	2 (3.6%)	1 (4.0%)	1 (7.1%)
ACTINIC KERATOSIS	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DERMATITIS CONTACT	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
DRY SKIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
ECCHYMOSIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
ERYTHEMA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)

Note: All doses received in a 21 day period is a course. All AEs that occurred from the start date of a course to the start date of the next course assigned to that course. AEs occurring after the end of the last course are included in the last course. All AEs occurring from the beginning of course 6 are included in the >= 6 Courses column.

Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.

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Luitpold Pharmaceuticals, Inc.
FCM
Revised Integrated Summary of Safety

Table 8.3
Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and FCM Courses Received
(VIT-4004 and VIT-5005 Studies)
Safety Population

	FCM (N = 199)					
	>= 1 Course (N=199)	>= 2 Courses (N=134)	>= 3 Courses (N=85)	>= 4 Courses (N=55)	>= 5 Courses (N=25)	>= 6 Courses (N=14)
HYPERHIDROSIS	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
NIGHT SWEATS	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PRURITUS	0 (0.0%)	0 (0.0%)	2 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PURPURA SENILE	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
RASH	0 (0.0%)	3 (2.2%)	1 (1.2%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
RASH PRURITIC	0 (0.0%)	0 (0.0%)	2 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SKIN DISCOLOURATION	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SKIN LESION	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SKIN ULCER	1 (0.5%)	3 (2.2%)	3 (3.5%)	0 (0.0%)	1 (4.0%)	0 (0.0%)
SWELLING FACE	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
VASCULAR DISORDERS	12 (6.0%)	2 (1.5%)	5 (5.9%)	3 (5.5%)	0 (0.0%)	1 (7.1%)
DEEP VEIN THROMBOSIS	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
EXTREMITY NECROSIS	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HAEMATOMA	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HYPERTENSION	3 (1.5%)	2 (1.5%)	4 (4.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HYPOTENSION	5 (2.5%)	0 (0.0%)	1 (1.2%)	1 (1.8%)	0 (0.0%)	1 (7.1%)
INTERMITTENT CLAUDICATION	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
JUGULAR VEIN DISTENSION	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
LYMPHOEDEMA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)

Note: All doses received in a 21 day period is a course. All AEs that occurred from the start date of a course to the start date of the next course assigned to that course. AEs occurring after the end of the last course are included in the last course. All AEs occurring from the beginning of course 6 are included in the >= 6 Courses column.

Subjects are counted once within System Organ Class and Preferred Term.
All percentages in this table are calculated using non-missing data only.

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Appendix B

Complete Analysis of Mortality in the FCM Clinical Program, Including Individual Case Summaries and Reviews of External, Independent Experts

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Complete Analysis of Mortality in the FCM Clinical Program, Including Individual Case Summaries and Reviews of External, Independent Experts

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1.0 INTRODUCTION

Eleven deaths were reported in the entire FCM development program. All eleven deaths were judged to be unrelated to study drug by Investigators.

This summary compiles an analysis of mortality in the FCM clinical program as well as providing individual summaries of each of the death cases including the evaluations of all external, independent reviewers. **Some of the information contained in Section 1.1 of this document was previously presented in Section 2.6.7 of the Complete Supporting Documentation from the Clinical Development Program on the Efficacy and Safety of FCM.** However, the information has been repeated in this Appendix with additional relevant information in order to present a comprehensive overview of the occurrence of death in the FCM studies. **This duplicate information is indicated throughout the document by "(Repeated)" next to the section title.**

Five deaths were reported following treatment with ferric carboxymaltose (FCM) and 1 death following treatment with iron sucrose in parallel-group controlled trials. In these postpartum and heavy uterine bleeding (HUB) studies, 1 postpartum subject died from autopsy-proven peripartum cardiomyopathy. Of the 4 remaining deaths following FCM, 3 were subjects with chronic kidney disease (CKD) and 1 was a subject with inflammatory bowel disease (IBD).

Five deaths were reported in uncontrolled studies: 4 subjects with CKD and 1 subject with iron deficiency anemia (IDA). The etiology of all the deaths was variable and no clinically important pattern was observed. All 11 deaths were judged to be unrelated to study drug.

An independent, external group of experts with expertise in iron therapeutics, clinical pharmacology, epidemiology, nephrology, cardiology and pathology was convened to assess the possible role of FCM treatment in the deaths. The group considered the possible relationship of dose, time between dose and event, phosphate levels, and reported cause of death. In addition, analytical challenges in comparing treatment groups across disparate populations were addressed by experts in statistics and epidemiology.

1.1 Analysis of Deaths

1.1.1 Comparability of Risk (Repeated)

Unbiased comparison of treatment groups for deaths must account for treatment group differences in numbers of subjects and length of observation, as well as treatment group differences in the baseline (intrinsic) mortality risk. There were over twice as many subjects exposed to FCM as in the control groups and the length of observation for FCM was over twice that of oral iron (**Table 1**). This difference arises from 2:1 randomization schedules and uncontrolled studies of FCM. Therefore, treatment group comparisons must focus on incidence rates and mortality rates per 100 patient years.

Table 1. Exposure in FCM Studies

Population	FCM		Control	
	Number of Subjects	Patient Years of Follow-up	Number of Subjects	Patient Years of Follow-up
Controlled Studies				
Postpartum/HUB	773	115.1	668	90.0
Hemodialysis	119	15.4	118	14.7
Nondialysis CKD	147	22.8	103	14.7
IBD	137	30.7	63	12.9
Chronic Heart Failure	30	6.4	42	8.5
Phase 1	24	0.5	8	0.2
Subtotal	*1230*	*190.9*	*1002*	*141.0*
Uncontrolled Studies				
	925[a]	119.1	0	0
Total	*2080[a]*	*310.0*	*1002*	*141.0*

HUB = heavy uterine bleeding, CKD = chronic kidney disease, IBD = inflammatory bowel disease
a There were 75 subjects who received FCM in both a controlled study and the uncontrolled extension study. Thus, there were 2080 unique exposures.

As seen in **Table 2**, the intrinsic risk of death varies substantially across the patient populations included in the development program. Mortality rates based on all combined studies are biased because the uncontrolled studies were conducted primarily in the high risk populations. Comparisons based on randomized controlled studies decrease this bias because the concurrent control provides an estimate of the intrinsic mortality risk in the population. However, the interpretation of mortality rates combined across disparate populations is uncertain. Treatment group comparisons are thus best made in combinations of randomized controlled studies with populations of similar intrinsic mortality risk.

Table 2. Baseline Mortality Risk and Mortality Risk Per 100 Patient Years for Specific Causes of Death in Specified Population Groups in the US

Specified Population Groups	Mortality Risk	Mortality Risk per 100 Patient Years
Hemodialysis[a]	18.6%	18.6
Non-dialysis Dependent Chronic Kidney Disease[b]	7.5%	7.5
Inflammatory Bowel Disease[c]	0.2%	0.2
Postpartum[d]	<0.0025%	0.0025
Heavy Uterine Bleeding	NR	NR

NR = not reported for mortality rate << 0.1 per 100,000 population in specified group.
Sources: Data derived and calculated from:
a: US Renal Data System (US Renal Data System 2006 Annual Report [www.usrds.org/adr.htm]).
b: AJKD 2005:46[5]
c: NIH (Everhart JE. Digestive diseases in the US: Epidemiology and Impact – National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of National Institute of Health (NIH) Publication No. 94-1447, 1994.)
d: CDC

In order to reduce the bias for treatment group comparisons, the primary population for mortality comparisons is the combined postpartum and HUB studies. These studies are in the targeted population, have low intrinsic baseline mortality risk, and have similar exposure/follow-up for the 2 treatment groups. The combination of all other parallel-group, randomized studies provides a supportive population for mortality comparisons. This population includes subjects with higher

baseline mortality risk such as chronic kidney disease (non-dialysis dependent and hemodialysis dependent), IBD, and heart failure. Patient-years of follow-up is also larger in the FCM group (75.8 years) as compared to the control group (51.1 years; **Table 3**). Finally, descriptive statistics are provided for the uncontrolled studies that include higher-risk subjects and lack a control group to estimate the intrinsic mortality risk for the study populations.

1.1.2 Observed Mortality Rate (Repeated)

A summary of the observed mortality rate is presented for each study population in **Table 3**. In general, the observed mortality rates are consistent with the baseline mortality risks in **Table 2**. Note that the patient-years of exposure for the population of uncontrolled studies are disproportionally influenced by subjects in Study VIT-05 who were followed up to 44 weeks. It is not clear whether the estimated mortality rate per 100 patient-years in this population could be biased as a result of combining this long follow-up with the shorter follow-up in the other uncontrolled studies.

Table 3. Observed Mortality Rate in FCM Clinical Program in Parallel-Group Studies

	Mortality Rate for FCM		Mortality Rate for Control Subjects[a,b]	
Population	**Total**	**Deaths/100 Patient Years**	**Total**	**Deaths/100 Patient Years**
Postpartum/HUB Studies	1/773 (0.13%)	0.87 (PY[c]=115.1)	0/668 (0)	0 (PY=90.0)
Other Controlled Studies	4/457 (0.88%)	5.28 (PY=75.8)	1/334 (0.30%)	1.96 (PY=51.1)
Uncontrolled Studies	5/925 (0.54%)	4.20 (PY=119.1)	NA	NA

HUB = heavy uterine bleeding
[a] Control excludes subjects from placebo-controlled crossover Study VIT-06 since subjects who received placebo in Study VIT-06 also received FCM within ±7 days of the placebo dose. Study VIT-06 had 279 postpartum/HUB subjects and 213 IBD/HD/ND-CKD subjects.
[b] Control group includes iron sucrose, oral iron, and placebo
[c] PY=Patient years

1.1.3 Nonclinical Evidence for Possible Mechanisms

A comprehensive program of nonclinical studies was performed for FCM. All studies were conducted in normal, non-anemic animals. Repeat-dose toxicity studies were conducted in rats and dogs with up to 26 weeks of treatment at doses of up to 30 mg Fe/kg/week with a 6 week recovery period in separate control and high dose animals. Repeat dose studies were also conducted in rats and dogs receiving doses of up to 90 mg Fe/kg/week for 13 weeks. Data from the repeated-dose toxicity studies have shown uptake and retention of iron in cells of the RES in major storage organs including liver, spleen and kidney. Toxicity was evident in both rats and dogs expressed mainly in altered hepatic function and in histopathologic changes in the liver. Altered kidney and red cell parameters were also evident.

A summary of nonclinical evidence for each putative mechanism of cardiac toxicity follows the abbreviated summaries of 4 chronic toxicity studies.

1. A chronic toxicity study (VFR070/042337) was conducted in beagle dogs at doses of 0, 1, 3, or 10 mg Fe/kg 3 times per week for 26 weeks equivalent to total doses of 0, 3, 9 or 30 mg Fe/kg with a 6 week recovery period in separate control and high dose animals. An additional Interim Phase group was also included in animals comprising the same control and treatment groups as in the Main Phase of the study which were treated for 13 weeks. Animals in the Main Phase were sacrificed after 26 weeks of treatment, while animals in the Interim Phase were sacrificed following 13 weeks of treatment. Control and high dose animals comprising the 6 week recovery group were sacrificed following 6 weeks of recovery. Blood samples were taken pre-treatment, during weeks 13 and 26 of treatment (before dosing) and week 6 of recovery. Blood samples were also taken during week 6 from Interim Phase animals only. Complete histopathology was performed on each animal with Perls' staining of selected tissues to confirm iron depositions. Electrocardiography and blood pressure tracings were recorded when possible at the same times on each animal during the pre-treatment period, during weeks 13 and 26, pre-dose, 2 and 24 hours after dosing and in recovery animals during week 6.

   There were no differences in chemistry parameters between treatment and control groups during week 6. Mid and high dose females showed significantly higher potassium levels as compared with controls during week 13 only. A significant increase in calcium was reported among high dose males relative to controls during week 26 only. High dose females showed a significant increase in calcium relative to controls during week 26. There were no significant differences in chemistry parameters among high dose and controls during week 6 of recovery.

   Differences in electrocardiogram and blood pressure tracings are considered within normal variations.

   Results of histopathology revealed expected treatment related appearance of pigmented macrophages (confirmed by Perls' Prussian blue stain) in a number of tissues including liver, spleen, parenteral injection sites, lymph nodes, adrenals, lungs, stomach, small intestines and bone marrow of the sternum. Iron pigment was also reported in the glomerular mesangial cells and interstitium of the kidneys, as also found in the rat. Pigmented macrophages were noted in the sternum of high dose dogs of the Interim Phase, Main Phase and Recovery Phase groups. There were no treatment related findings in the heart from the animals of the 3 study phases.

   Apart from slight differences in electrocardiography and blood pressure recordings, which are likely attributable to normal variations in dogs, there were no reported treatment related effects on the cardiovascular system in the dogs treated with FCM for up to 26 weeks.

2. The systemic toxicity of FCM was assessed in rats (VFR 071/043284) following intravenous (bolus) administration of FCM for 13 weeks at doses of 0, 1, 3, 10, or 30 mg Fe/kg 3 times a week equivalent to 0, 3, 9, 30, or 90 mg Fe/kg/week. Each control and dosage group consisted of 10 male and 10 female CD rats.

   Blood samples were obtained during weeks 4 and 13. All animals were sacrificed at the end of the 13 week treatment period with complete necropsies. Histopathology was performed on all major tissues from all animals.

   Lower levels of phosphorus (statistically significant) were reported in week 13 for males and females of the 2 highest dose groups (30 and 90 mg Fe/kg/week). Calcium levels

were not remarkably different in males or in females during either the 4 or 13 week time periods. However the levels were statistically significantly higher among females of the highest dose (90 mg Fe/kg/week) group during week 4 but not week 13 and they were statistically significantly lower in the 30 mg Fe/kg/week group only during week 13 relative to controls.

The expected deposition of brown pigment in macrophages was observed in liver, spleen, kidney, lymph nodes, bone, and heart in the highest dose group (90 mg Fe/kg/week). Slight deposition of brown pigment was also observed in the sternum of 2 of 10 females of the 30 mg Fe/kg/week dose group and in the femur of 1 of 10 females from the same dose group. Perl's stain methodology in liver, spleen and kidney confirmed the brown pigment contained ferric iron. There were no other histopathologic changes reported in the heart.

Based upon the parameters assessed in this study and the results of histopathology, there were no apparent cardiovascular effects noted in the rats treated with FCM for up to 13 weeks.

3. Another chronic toxicity study (VFR 072/052022) was conducted in rats at doses of 0, 1, 3 or 10 mgFe/kg 3 times a week (0, 3, 9 or 30 mgFe/kg/week for 26 weeks) with 6 weeks of recovery in separate control and high dose animals. Blood samples were taken for chemistry and hematology determinations before dosing during weeks 13 and 26 of treatment and after 6 weeks of recovery. Histopathologic examinations included the kidney and other organs including liver, spleen, adrenals, lymph nodes, bone marrow, heart and the gastrointestinal tract.

   Slight but significantly increased calcium levels from blood chemistry evaluations were reported among both sexes of the high dose group during weeks 13 and 26. An increase in potassium was also noted in males only during week 13 and in females only during week 26. A slight but significant increase in phosphorous level was reported only in females and only during week 13 of treatment. Sodium and chloride levels were slightly but significantly decreased in both males and females during week 13 of treatment, with a significant increase in sodium in males only during treatment week 26.

   Changes in total sodium and chloride were inconsistent however slight but significantly reduced levels were reported in males only during week 26 of treatment.

   Apart from the brown pigment deposition in macrophages of kidneys, heart and bone marrow and similar deposition in glomerular mesangial cells and in cortical tubular epithelium of the kidney, there were no reported histopathological changes associated with treatment at any dose level.

4. A thirteen week toxicity study (VFR041/993362) was conducted in beagle dogs receiving single weekly doses of 0, 9, 30, or 90 mg Fe/kg/week by intravenous infusion. All animals were observed daily for clinical signs, with electrocardiogram and blood pressure recordings taken before dosing, on Day 1 and Week 13 of dosing. Blood samples were taken before dosing and during Weeks 6 and 13. All animals were sacrificed at the end of the treatment period with complete necropsies and histopathology.

   Males and females receiving 30 or 90 mg Fe/kg/week and males of the 30 mg Fe/kg/week group showed reductions in hemoglobin concentrations during week 13. There were no

significant changes in phosphorus or calcium determinations in either sex at either time point in the study.

There were no treatment related changes in electrocardiography or blood pressure recordings.

There were some minimal to moderate amounts of brown pigment deposition noted in macrophages of the femur and sternum in males and females of the 30 and 90 mg Fe/kg/week dose groups. There were also brown pigment deposition in macrophages in various sections of the heart in males and females of the 30 and 90 mg Fe/kg/week dose groups. There were no histopathological changes reported in the heart of rats or dogs other than the brown pigment deposition at the highest dose groups.

1.1.3.1 Blood Pressure and Heart Rate

The potential cardiovascular effects of FCM were evaluated in a safety pharmacology study with beagle dogs receiving single intravenous doses of either 30 or 90 mgFe/kg. In this study entitled "Telemetric Evaluation of Cardiovascular Effects in the Conscious Dog" (VFR 066/042584), there were no adverse effects at either dose level on arterial blood pressure (systolic, diastolic and mean), or heart rate. In study VFR070/42337 there were also no treatment related differences in blood pressure and heart rate parameters.

1.1.3.2 Edema

Edema was not reported as a clinical finding among rats or dogs treated with FCM for up to 26 weeks.

1.1.3.3 Electrolyte Change

Although there were some electrolyte changes reported among rats and to a lesser extent among dogs treated for up to 26 weeks with up to 30 mg Fe/kg/week, they are not clinically meaningful and do not predict a risk for altered cardiac conduction or rhythm.

1.1.3.4 Cardiac Conduction and Rhythm

The potential cardiovascular effects of FCM were evaluated in a safety pharmacology study with Beagle dogs receiving single intravenous doses of either 30 or 90 mgFe/kg (study VFR 066/042584). There was no evidence of treatment-related prolongation of QT interval, indicating no adverse effects on ventricular depolarization. In addition there were no abnormal ECG rhythm or morphology changes related to treatment at either dose level. Electrocardiography recordings in dogs treated for 26 weeks with up to 30 mg Fe/kg/week or following a 6 week recovery period appeared within normal variations for beagle dogs.

No electrolyte imbalances were seen in the chronic toxicity studies that might predict a risk for altered cardiac conduction and rhythm.

There were no histopathological changes reported in the heart of rats or dogs other than brown pigment deposition at the highest dose groups.

1.1.3.5 Rate of Hemoglobin Rise/Maximum Hemoglobin

The nonclinical program was conducted in nonanemic animals, therefore, evaluations on the impact of hemoglobin rise on safety could not be assessed as there were no consistent treatment related increases.

1.1.3.6 Summary of Nonclinical Program

In summary, the results of single dose studies in dogs of up to 90 mg Fe/kg/week and chronic toxicity studies in normal non-anemic rats and dogs treated for up to 26 weeks at doses of up to 30 mg Fe/kg/week demonstrate no findings that predict a risk for cardiac toxicity of FCM. The chronic toxicity doses studied were significantly higher than the 1,000 mg Fe (up to a maximum of 15 mg/kg Fe) per week for 1 to 3 weeks utilized in the FCM human development program.

1.1.4 Clinical Evidence for Possible Mechanisms (Repeated)

The potential predictive value of anaphylaxis, bioactive iron reactions, rate of hemoglobin rise, hemoglobin >13 g/dL, hypophosphatemia, baseline mortality risk and FCM dose on the mortality rate was explored.

No death was consistent with the expected timing of anaphylaxis or bioactive iron reactions in relation to FCM administration. No death was consistent with an allergic, anaphylactic, or bioactive iron reaction mechanism. No patient administered FCM demonstrated allergic reactions consistent with anaphylaxis. No patient administered FCM in clinical trials has demonstrated symptoms or findings consistent with bioactive iron reaction. The absence of bioactive iron reactions after rapid administration of high doses of FCM confirms in vitro information that iron in FCM is tightly bound and, in serum, is not dialyzable or available for donation to transferrin.

Rate of rise in hemoglobin during the study had no negative effect on the serious adverse event rate in FCM clinical trials. No patient receiving FCM was simultaneously initiated on epoetin therapy, the presumptive causal agent in adverse cardiovascular events related to rapid hemoglobin rise in patients with chronic kidney disease. Rapid hemoglobin rise was commonly seen after either FCM or oral iron treatment, but as expected, hypertension, hypertensive emergencies, and signs of fluid overload were not seen. One hypertensive hemodialysis subject had a rapid rise with hemoglobin reaching 10.1 g/dL, 8 days prior to death (see Section 5.2.1 for case discussion). No other death cases had a rapid rise in hemoglobin. Those deaths that occurred before follow-up hemoglobin could be obtained would have also occurred before hemoglobin could have risen significantly, if at all.

Serious adverse event rates were convincingly associated with lower rather than higher observed hemoglobin levels, presumably reflecting the increased disease burden associated with severe anemia. Administration of iron, unlike administration of ESAs, does not stimulate erythropoiesis, but rather facilitates the restoration of erythropoiesis to normal levels. Thus, iron therapy in any form cannot generate hemoglobin levels above what is physiologically normal for the patient, and therefore cannot generate "excessive" hemoglobin levels. If the patient receives more iron than is needed to restore the hemoglobin to normal, the hemoglobin does not rise further. Rather, the excessive iron is stored for future use.

The deaths occurred in subjects for whom the observed phosphate values at the time of the serious adverse event leading to death were not significantly low, or in subjects whose death occurred too early after FCM administration for hypophosphatemia to have developed.

The mortality rate was related primarily to the baseline mortality risk (as shown in **Table 2**) of the clinical trial populations (**Table 4**). That is, the mortality rate was highest in the HD and ND-CKD populations and lowest in the postpartum and HUB populations.

Table 4. Mortality by Baseline Mortality Risk in Parallel-Group Controlled Studies

Population	FCM Incidence	Control Incidence	Probability of No Control Deaths[a]	Fisher's Exact Test[b]
PP/HUB	1/773 (0.13%)	0/668	41.9%	>0.9999
HD	1/119 (0.84%)	0/118	37.0%	>0.9999
ND-CKD	2/147 (1.36%)	0/103	24.4%	0.5135
IBD	1/137 (0.73%)	0/63	63.0%	>0.9999
CHF	0/30	1/42 (2.38%)	NA	>0.9999

PP = postpartum; HUB = heavy uterine bleeding; HD = hemodialysis; ND-CKD = non-dialysis dependent chronic kidney disease; IBD = inflammatory bowel disease; CHF = congestive heart failure
a Given observed rate for FCM
b Comparing FCM vs control

Because the risk of infection in CKD patients is high we also investigated any association between infection and mortality. The overall incidences of adverse events or serious adverse events associated with infections were similar between FCM and controls. In the key patient population currently receiving high doses of intravenous iron, anemic patients with chronic kidney disease undergoing chronic hemodialysis, the evidence is conclusive that there is no link between intravenous iron administration and infection. Though hemodialysis patients are prone to infection and receive an average of 3.1 grams of intravenous iron annually,[1] prospective observational trials,[2] randomized controlled trials,[2] and retrospective analysis of large scale United States dialysis databases[3] have failed to demonstrate a relationship between intravenous iron administration and risk of infection.

Among subjects treated with FCM, the number of doses received ranged from 1 to 11; however, the majority of the subjects received ≤3 doses of FCM. The overall observed mortality rate did not appear related to number of doses, total dose, maximum single dose, or last single dose received prior to death as shown in **Table 5**.

Table 5. Crude Mortality Risk by Level of FCM Exposure

FCM Exposure	Total Deaths	Total FCM Subjects	Crude Mortality Risk
Number of Doses			
1	5	723	**0.69%**
2-3	3	989	0.30%
4-5	1	88	1.14%
6-7	1	195	0.51%
8-9	0	74	0
10-11	0	11	0
Total Dose			
0 -1000 mg	6	812	**0.74%**
1001 to 1400 mg	1	619	0.16%
>1400 mg	3	649	0.46%
Maximum Single Dose			
<400 mg	3	331	**0.91%**
400-499 mg	0	1	0
500-599 mg	0	41	0
600-799 mg	0	158	0
800-999 mg	0	475	0
1000 mg	7	1074	0.65%
Last Single Dose			
<500 mg	3	718	0.42%
500 mg	3	302	**0.99%**
501-999 mg	0	514	0
1000 mg	4	546	0.73%

The highest observed mortality rate within each category is **bolded**.

1.1.5 Cardiac Conduction and Rhythm

Six studies in the FCM development program (CL-02, VIT-09, CL-15, VIT-53214, CL-03, and CL-08) required ECG's at baseline and post FCM dosing, including 1 study in subjects with postpartum anemia (VIT-09) and 1 study that required 48-hour telemetry data (CL-02). The ECG data were obtained in 1,022 subjects, 715 of whom had been treated with FCM. Forty-eight hour telemetry data were collected in 32 subjects, 24 of whom were treated with FCM.

No safety issues have arisen from the ECG or telemetry data. No single preferred term related to cardiac conduction or rhythm was observed for >1% of subjects administered FCM. No pattern among the deaths suggest a mechanism related to cardiac conduction or rhythm.

1.1.6 Probabilistic Assessments (Repeated)

Given the observed mortality rate for FCM, the probability of the observed number or fewer deaths for the control group is high as shown in **Table 6**. The probability of no deaths in the control group in postpartum/HUB is 41.9% and the probability of 1 or fewer deaths in the control group for other controlled studies is 20.7%.

Table 6. Probability of Observed or Fewer Number of Deaths in the Control Group in Each Population When Observed Mortality Rate Equals That Observed for FCM

	Population-specific Mortality Rate			
Study Status Population	**FCM Rate**	**Observed Control Deaths**	**Number of Control Subjects[1]**	**Probability of Observed or Fewer Deaths**
Postpartum/HUB	1/773 (0.13%)	0	668	41.9%
Other Controlled Studies[2]	4/457 (0.88%)	1	334	20.7%

HUB = heavy uterine bleeding

1 Control excludes subjects from placebo-controlled crossover Study VIT-06 since subjects who received placebo in Study VIT-06 also received FCM within ±7 days of the placebo dose. Study VIT-06 had 279 postpartum/HUB subjects and 213 IBD/HD/ND-CKD subjects.

2 Control group includes iron sucrose, oral iron, and placebo

1.1.7 Inferential Analyses for All Cause and Cardiac Mortality (Repeated)

Restricting the comparison of FCM to control in the randomized controlled trials reduces the bias on including data from non-controlled trials and supports a more objective comparison. The randomized controlled trials population provides an estimate of the intrinsic death rate and via randomization reduces systematic bias between treatments. This does not eliminate difficulties in interpretation since the rate difference is small and there are methodological challenges with combining medically disparate populations. The observed incidence rates in the randomized controlled trials for all cause mortality, all cause mortality within 30 days after the last dose of study drug, and cardiac mortality are small and the differences between treatment groups are also small as shown in **Table 7**. In addition, the 95% exact confidence intervals for the odds ratio of FCM versus control are wide for each observed mortality rate indicating substantial uncertainty regarding the existence of a mortality risk.

Table 7. Inferential Analysis for All Cause and Cardiac Mortality in All Randomized Controlled Parallel-Group Trials

Mortality Endpoint	FCM Rate	Control Rate	Odds Ratio (CI)[1,2]	P-value[3]
All Cause	5/1230	1/1002	4.1 (0.5, 193.4)	0.2328
All Cause <30 days	4/1230	1/1002	3.3 (0.3, 161.0)	0.3874
Cardiac	3/1230	1/1002	2.4 (0.2, 128.6)	0.6325

Includes Studies VIT-11, VIT-01, VIT-09, VIT-02/VIT-03, CL-15, CL-08, VIT-04, CL-02 and CARS

[1] Odds ratio for FCM vs. control (>1 indicates worse mortality for FCM)

[2] CI = Exact 95% confidence interval on odds ratio

[3] Fisher's exact test for FCM vs. Controls

In the FCM clinical program, 1 FCM subject died in the postpartum/HUB randomized controlled trials (RCTs), 4 FCM subjects and 1 control subject died in the other RCTs, and 5 FCM subjects died in the uncontrolled studies.

2.0 DEATHS IN FCM SUBJECT IN POSTPARTUM AND HUB RANDOMIZED CONTROLLED TRIALS

2.1 Overview of Deaths in FCM Subjects in Postpartum and HUB Randomized Controlled Trials

Indication/ Study/ID/ Country	Investigator Assessment of Cause of Death	External, Independent Experts Assessments of Probable Cause of Death	Age/ Sex/ Race	Last dose of FCM -mg	Time since last dose -days
Postpartum/ VIT-01/ Case 1 RCT/ US	**Peripartum cardiomyopathy (PPCM) with heart failure, autopsy proven**	• *Current Illnesses:* obesity • *Past Hx*: multiparity, postpartum anemia with previous pregnancy • *Cause of death:* autopsy-confirmed peripartum dilated cardiomyopathy. Autopsy excluded AMI, valvular disease, hypersensitivity myocarditis & pulmonary embolus. • *Pathogenesis:* Idiopathic, early onset, often fatal. Frequency of death 6.4x greater in African Americans. Patient had the 3 strongest risk factors for PPCM, and the 3 strongest risk factors for fatal outcome of PPCM: African American, obese, multiparous x 4. • *Link to any iron agent, including FCM*: none, other iron related causes of dilated cardiomyopathy excluded. In preclinical toxicology studies, no adverse cardiac findings. • *Link to other trial deaths*: None	27/ F/ B	1,000	8

Bold= cases of probable cardiac etiology.

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2.2 Case 1 RCT

Study Number: VIT-01
Event: Peripartum cardiomyopathy with heart failure

This 27-year-old black female with postpartum anemia requiring iron supplementation was randomized to intravenous iron on July 14, 2005. Her history is significant for being multiparous (4), obese (pre-pregnancy weight of 228 pounds), requiring a blood transfusion for anemia during a 1999 pregnancy and having an uncomplicated vaginal delivery on [redacted] She had a long history of microcytic hypochromic anemia, and no prior history of recognizable heart disease. Her baseline hemoglobin on [redacted] was 7.9 g/dL with a TSAT of 5% and ferritin of 5.6 ng/mL. Her labs other than hematologic parameters consistent with iron deficiency anemia were unremarkable. In the 3 days between screening and baseline, the subject gained 1.3 kg (90.9 kg to 92.2 kg), which is unusual during the early postpartum period. This patient also reported a very low score for the vitality component of the SF-36 quality of life assessment.

She received her first dose of 1000 mg. FCM on study day 0. Her vital signs were within normal limits, and showed no apparent evidence of cardiac abnormality. On study day 7 she did not keep her appointment with the clinic. On study day 8, 14 days after parturition, her friend found her unresponsive at her home in bed with "frothy edema fluid" from her mouth. EMR was called; they tried to resuscitate her but were unsuccessful. She was dead on arrival at the hospital. An autopsy was done with the following findings: dilated left ventricle, moderate bilateral pleural effusions, pulmonary edema, and soft tissue edema. No cardiac iron deposition or eosinophilic myocardial infiltrates were found. There were no other organ abnormalities found. Blood alcohol was negative.

The coroner wrote the following in the summary/interpretation section of the autopsy report: "It is my opinion that death resulted from peripartum 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%." The cause of death is listed as peripartum cardiomyopathy with heart failure.

The Investigator considers this serious adverse event (peripartum cardiomyopathy with heart failure) unrelated to study drug.

2.2.1 Medical Monitor Literature Summary

For reasons that remain unclear, the postpartum period is associated with the relatively sudden onset of cardiomyopathy in healthy women without evidence of prior cardiac disease. Peripartum cardiomyopathy (PPCM) is a form of dilated cardiomyopathy with left ventricular systolic dysfunction that results in signs and symptoms of heart failure.[4] Estimates indicate that PPCM occurs in up to 1 of 4000 pregnancies and is more common in women who are African-Americans, obese, age > 30 years and multiparous.[5] Whitehead et al.[6] utilized data from the Centers for Disease Control (CDC) and Prevention's Pregnancy Mortality Surveillance System to examine pregnancy-related deaths due to cardiomyopathy from 1991 through 1997. The cause-specific pregnancy-related mortality ratio was 0.88 per 100,000 live births. Black women were 6.4 times as likely to die from cardiomyopathy as white women. Among PPCM cases in which

the interval from the end of pregnancy was known 48% died within 42 days of delivery. Reported mortality rates for PPCM range from 10% to 56%.

Proposed etiologies include viral, immunologic, toxic, and genetic factors, but in most cases no specific cause is found.[5] Symptom onset is variable as is the severity of the cardiomyopathy. Onset is usually days to weeks after delivery, and symptoms range from mild fatigue to acute pulmonary edema. PPCM is often unrecognized in its milder form, leading to the consensus that the condition may be more prevalent than reported.

2.2.2 Sponsor Commentary 1-30-07

Key data for Case 1 RCT are summarized in **Table 8**. This is a 27-year-old woman who died 14 days after delivery from PPCM. The patient had strong risk factors for PPCM (black, obese, multiparous) and the most potent risk factors for a fatal outcome of PPCM (black, multiparous). Her presentation with signs of acute heart failure and the timing of death was consistent with PPCM. Finally, the autopsy conclusively established the cause of death as PPCM.

No etiology potentially related to administration of either FCM or any class of intravenous iron agent is compatible with this patient's presentation and autopsy findings. The decline in serum phosphate seen after administration of FCM in women with postpartum anemia is modest and the nadir occurs later; that is, the median time to nadir is 14 days after initiation of therapy. Linear regression analysis from the VIT-01 postpartum trial yields a projected serum phosphate decline of only 0.55 mg/dL (95% confidence interval -1.89 to 0.78) at study Day 7 after initiation of FCM therapy. Since this patient's baseline serum phosphate was 3.9, her lowest projected phosphate within the 95% confidence interval would have been >2.0 g/dL, a level that is not associated with symptoms or findings of hypophosphatemia.

Similarly, although a rapid rise in hemoglobin after administration of epoetin alfa has been associated with hypertension in patients with chronic kidney disease, no epoetin alfa was administered in this patient and no evidence of either chronic kidney disease or hypertension was present at baseline. No hypertension has been described after correction of iron deficiency anemia by FCM or other intravenous iron administration. No increase in blood pressure was observed in the VIT-01 study after either FCM administration or oral iron administration in women with postpartum anemia, despite very rapid hemoglobin increases in both treatment groups. Specifically, 83.5% of subjects in the FCM safety population and 81.0% of their counterparts receiving oral iron (ferrous sulfate 325 mg thrice daily) showed an increase in hemoglobin ≥1.0 g/dL between baseline and study Day 7. Even in the absence of therapy, hemoglobin is expected to rise rapidly after parturition, without hypertension, due to a physiologic post-partum diuresis with plasma volume contraction. There is no clinical evidence based on assessment of serious and non-serious adverse events to support a concern that rate of rise in hemoglobin following intravenous iron supplementation in this patient population is a clinical concern.

Table 8. Chronology of Dosing and Selected Data for Case 1 RCT

Study Subject	Age/ Sex/ Race	Date	Time	FCM Dose (mg)	B/P Sys/Dia (mmHg)	Blood Chemistry PO4 (mg/dL)	Na (mEq/L)	K (mEq/L)	Ca (mg/dL)	Hgb (g/dL)	Adverse Event Preferred Term	Stop Date (RxEday)
VIT-01 Case 1 RCT	27/F/B		13:17			4.1	142	3.3	9.4	7.9		
			14:30			3.9	146	4.1	9.4	7.9		
			15:20		122/78 Sit 118/78 Sup							
			15:32	1,000								
			15:48		118/78 Sit 118/84 Sup							
			16:18		118/76 Sit 120/74 Sup							
			16:48		120/78 Sit 116/78 Sup							
			NR								Cardiac failure Peripartum cardiomyo-pathy	

Sys = systolic, Dia = diastolic, PO4 = phosphate, Na = sodium, K = potassium, Ca = calcium, Hgb = hemoglobin, RxEday = days since final dose of study drug, M = male, F = female, B = Black, C = Caucasian, NC = not collected, NR = not reported, Sit = sitting, Sup = supine, Std = standing

2.2.3 Independent Expert Review

Two independent experts (cardiologist Leslie T. Cooper, MD, Professor of Medicine, Mayo Clinic who is an expert in myocarditis and cardiomyopathies and anatomic/surgical pathologist Nancy Phillips, MD, Associate Professor, St. Louis University) reviewed this case and addressed whether or not they agreed with the pathologist's opinion that "death resulted from PPCM with heart failure" providing reasons and literature supporting their opinion and commenting on whether the etiology of the cardiomyopathy may have been myocarditis.

Dr. Leslie Cooper:

The diagnosis of PPCM is a diagnosis of exclusion. The onset of cardiomyopathy must be within the last month of pregnancy or the first 5 months following delivery, and other causes for heart failure must be excluded. The heart in this case was described as "dilated" and "flabby," which supports a diagnosis of cardiomyopathy as the cause of pulmonary edema. This patient had no prior history of recognizable heart disease, and coronary artery, congenital and valvular heart diseases were excluded at autopsy. An acute allergic or hypersensitivity reaction would usually have had an eosinophilic infiltrate, which was not present. The histopathologic findings in PPCM are variable. In a large series from Johns Hopkins Hospital, 63% of PPCM cases had myocarditis; however, the rate of inflammation is much lower in other series. Therefore, the absence of myocarditis in this case neither supports nor refutes a clinical diagnosis of PPCM.

Although the findings on autopsy in the context of the documented lack of prior cardiovascular disease support a diagnosis of PPCM, several features of the case are unusual. Multiparity and African American race are recognized risk factors for PPCM; however, she lacked other risk actors including pre-eclampsia, gestational hypertension, and advanced maternal age. Most cases of PPCM present with acute heart failure and improve with standard heart failure care. I

was not provided any clinical data after the baseline study visit, and therefore cannot comment as to whether the patient had a typical or atypical clinical presentation. No toxicology screen was provided, and therefore a toxic effect of cocaine or amphetamine cannot be completely excluded from the available data. The microscopic evaluation of the heart did not comment on the presence or absence of acute ischemia, which can occur with normal epicardial coronary arteries in the setting of severe spasm.

Toxic cardiomyopathy is an uncommon form of cardiac inflammation, characterized by direct myocyte toxicity. Antineoplastic agents including cyclophosphamide, anthracyclines, cocaine, arsenicals, fluorouracil have been associated with this type of reaction. Although many cases of drug-related myocarditis are obvious on standard hematoxylin and eosin stained sections, some cases are only diagnosed by electron microscopy. For example, examination of heart specimens in anthracycline-induced cardiomyopathy with electron microscopy demonstrates characteristic changes, including extensive depletion of myofibrillary bundles, myofibrillar lysis, distortion and disruption of the Z-lines, mitochondrial disruption and intramyocyte vacuolization. Because electron microscopy was not performed in this case, a toxic myocarditis cannot be completely excluded from the available data.

In summary, the data presented are most consistent with a diagnosis of PPCM; however, in the absence of a toxicology screen, clinical data from the days prior to her death and electron microscopy of the heart tissue, an acute cardiac toxic reaction due to one of the compounds described above, such as cocaine, and coronary spasm-related ischemia cannot be excluded".

Dr. Nancy Phillips:

Records available: autopsy report, ER visits and admission for parturition postpartum study visit records large volume of outpatient reports 1991 to 2002.

Past medical history: includes long history of microcytic hypochromic anemia, with at least one set of iron studies c/w iron deficiency anemia. She had a motor vehicle accident 11 years prior, cholecystectomy, no other non-gyn surgery. No history of asthma, diabetes (no significant elevations of glucose in record), heart disease. Several abnormal Pap smears including high-grade squamous intraepithelial lesion (HGSIL), several biopsies and colposcopies. Patient seemed to have poor compliance in her gynecologic visits from about age 17 onwards – also difficult to reach – had certified letters sent to her because there was no other way to contact her for follow-up of her HGSIL.

Current gestation: No records of outpatient prenatal care for this gestation. One ER visit at 32 wks for h/o one episode spotting (ceased) and new abdominal pain, exam showed no contractions, nondilated cervix. U/A clear, d/c. One ER visit for vaginal discharge, shown to be Candidiasis. BP, HR, RR all within normal limits. No edema, clubbing of digits, or jugular distension.

Delivery to discharge: initiation of 1st stage labor ~11:00 AM. Fast 2nd stage (~1 hr), delivery 01:22 AM, placenta delivered spontaneously without excessive bleeding. No generalized or spinal anesthesia. Patient weight 229# predelivery, 207# post-delivery. Patient noted to be anemic (hypochromic microcytic c/w insufficient iron). Other labs not significantly abnormal when repeated. No time course for anemia. Discharge, ibuprofen, depo-provera were discharge meds (depo shot administered before discharge). Seen for study and no complaints at that time, Review of systems negative.

Weight 203#. Drug/placebo study item administered, patient observed over 1 hr, all blood pressures and heart rates within normal limits pre and post drug.

found in bed with frothy edema fluid from her mouth, unresponsive to EMT person, CPR. So, unwitnessed death, time of death was ?.

Autopsy:

Main features: Pleural effusions, bilateral, "serosanguinous", volume "moderate" (no cc given) "Soft tissue edema" (no exact weight, no record of extremity pitting or non-pitting Lungs R 690 gm (normal mean weight 450 gm), L 620 gm (normal mean weight 375 gm): frothy edema in large airways, edema fluid on cut section. Pertinent negatives : no pulmonary embolus, no pneumonia. Microscopic exam: congestion and edema.

Heart, 320 gm (normal mean weight 270 gm, standard deviation 30 gm, for 168 cm woman), "flat", "left ventricle dilated but not thickened" (no measurements). Coronary arteries not narrowed. No mention of valves. This would have been a pertinent negative, eg, if there were mitral valve prolapse. Heart weight is modest for a dilated cardiomyopathy, but massive ventricular dilation and weight gain is a gradual process. An acute event would have merely a slightly heavy heart with a slightly dilated flabby left ventricle. Microscopic exam: no inflammation, no fibrosis, coronary arteries not narrowed.

Brain, kidneys, spleen, liver edematous

Liver steatosis, microvesicular (no % given, but was probably >33%, given the description of yellowish appearance grossly) – this is likely a chronic phenomenon, possibly due to ethanol use, possibly the herald of a metabolic syndrome X often associated with obesity. At any rate, it is not contributory to death. Patient not diabetic.

Toxicology screen: negative for alcohol. The tox. screen did not address cocaine and amphetamine derivatives (cocaine dilated cardiomyopathy, coronary artery spasm, etc). I would have preferred a larger tox. screen, though the half-lives of the cocaines/amphetamines are quite short, and I suspect that was why they weren't ordered on an unwitnessed death.

The autopsy is not very detailed, so I can't evaluate degree of left ventricular dilatation, nor is there a way to determine weight gain since last exam (measure of degree of generalized edema).

Patient appeared to have a cardiac etiology for death, due to the presence of edema and absence of any history of renal failure. Patient did have a history of use of furosemide and potassium supplements at the exam. However, she was not issued prescription for same on discharge after the birth, nor was there evidence of administration during labor. Blood pressure, heart rate, respiratory rate at all normal. No weight gain (in fact, 4# loss) between discharge and visit for study. Therefore there was no obvious evidence for cardiac failure during the peripartum period, last observation 7 days (or less?) before death.

Likely cause of death: Dilated cardiomyopathy. Clinical findings, not histologic findings, establish the likely etiology of the cardiomyopathy.

Possibilities include:

- *Dilated cardiomyopathy associated with pregnancy/ postpartum status*

- *Dilated cardiomyopathy associated with viral syndrome (not all will have recognizable inflammation of myocardium)*

We have evidence of postpartum state, therefore the former seems more likely than the latter.

Possibilities not documentable:

- *Dilated cardiomyopathy, cocaine-associated (requires toxicology not obtained)*

Unlikely :

- *Mitral valve prolapse with or without chordae tendinae tear. There was no gross description of the valves in the autopsy report. I would assume that a tear would have been described in the pathology report, if present, but the mitral valve prolapse without chordae tear is often a subtle finding at postmortem. About 2% of sudden deaths in this age group due to MVP.*

Ruled out:

Patient knew she had a shellfish allergy, and had a mild allergy to Percocet (hives), but anaphylaxis would present as airway obstruction, and usually hyperinflation, rather than uniform pulmonary edema. Patient had no history of asthma, which would also present as airway obstruction and hyperinflation.

Some common causes of sudden death in adults are clearly ruled out: massive pulmonary embolus, massive hemorrhage (not noted on death scene report, and uterus was intact), intracranial bleeding due to aneurysm rupture. Uncommon cardiac sudden death cause also ruled out: arteritis was not observed on coronary sectioning".

Independent Clinical Pharmacologist Safety Expert Dr. Judith Jones, MD, PhD and Staff, Degge Group:

Because of her having three major risk factors for post-partum cardiomyopathy, including the conclusion at autopsy, this appears to be the most likely explanation. Tidswell et al, 2004,[5] Rate: 1/4000; risk factors: obesity, age >30, black, multipara. Patient had 3/4 risk factors. Whitehead et al, 2003,[6] the frequency is 6.4 times greater in black than caucasian women. Of cases reviewed, 48% died within 42 days of delivery-patient died 14 days after delivery. The occurrence of her sudden death due to this disorder (although it is frequently fatal) may have related to additional factors where there is no data on their status near the time of death. These include: (1) hypokalemia (which was documented in screening); (2) her anemia, which certainly independently contributed to her heart failure and (3) restarting her Inderide, which might also have contributed, or not (error, see above). There does not appear to be any suggestions that the FCM injection contributed to this outcome.

2.2.4 Sponsor Commentary 4-27-07

This is a 27-year-old woman who died 14 days after delivery and 8 days after a single dose of FCM from peripartum cardiomyopathy (PPCM). The patient had strong risk factors for PPCM (black, obese, multiparous) and the most potent risk factors for a fatal outcome of PPCM (black, multiparous). Her presentation with signs of acute heart failure, the timing of death and absence of demonstrable heart disease before the last month of pregnancy was consistent with PPCM.

Autopsy and post mortem histopathology demonstrated dilated cardiomyopathy as the cause of the pulmonary edema with no other organ abnormalities, consistent with PPCM. The autopsy, post mortem histopathology, clinical details on this patient and known literature effectively exclude alternative, theoretical, iron related etiologies for a dilated cardiomyopathy including the following:

- *Hypersensitivity myocarditis (*also called eosinophilic myocarditis): As stated by Dr. Cooper (a myocarditis expert), in his review of this case, the lack of an eosinophilic myocardial infiltrate on autopsy excludes this mechanism.

- *Ischemic cardiomyopathy due to atherosclerosis:* The subject's autopsy demonstrated no atherosclerotic disease in the coronary arteries.

- *Ischemic cardiomyopathy due to coronary spasm such as that seen with cocaine:* Toxic free iron administered intravenously produces immediate hypotension secondary to direct vasodilation.[7] Vasodilation, not vasoconstriction, characterizes intravenous iron labile iron reactions (FCM or iron sucrose, particularly). Moreover, vasomotor changes after intravenous iron administration are acute and transient. This subject demonstrated no clinical evidence of vasoconstriction (as reflected by BP changes) during or after intravenous administration of ferric carboxymaltose.

- *Iron overload cardiomyopathy:* Cardiomyopathy secondary to hereditary hemochromatosis or transfusional hemosiderosis in β-thalassemia major develops only after many years of exposure to tissue iron excess, presents with thickened ventricular walls usually as a restrictive rather than dilated cardiomyopathy, and is characterized by grossly visible iron deposits and intense tissue iron staining histiologically.[8,9] This subject had no ventricular wall thickening or report of iron staining. Dr. Liu[9] in a review of iron overload cardiomyopathies states: "the iron preferentially deposits initially in the epicardium, only later to involve the transmural wall thickness. This is thought to explain the preservation of systolic ventricular function for a significant period of time despite relatively high iron levels." As iron accumulates in the heart there is also progressive damage to other organs with fibrosis in the liver and multiple endocrine organs.[9,10] Patients who have iron deposits in the myocardium almost always have deposits in other organs.[8] The subject's autopsy reported no iron staining or fibrosis in any organ.

- *Acute iron-mediated cardiotoxic effect*: Fatal overdose with oral iron salts (consisting of all free iron) presents abruptly after ingestion with multisystem failure, metabolic acidosis and shock. No such syndrome has been seen after intravenous administration of colloidal iron-carbohydrate agents of any class, even following overdoses of very large doses. In FCM clinical trials, no evidence of non-fatal organ toxicity was demonstrated for any organ system, including cardiac and the subject's autopsy revealed no evidence of other organ system pathology. After oral iron overdose, stainable cardiac iron may be seen on histopathology. Siderotic staining is not seen after chronic administration of intravenous iron dextran in dialysis patients (after an average of 5.5 (SD 0.9) grams of iron dextran),[11] and no siderotic staining was seen in cardiac histopathology in this subject.

- *Oxidative stress due to Iron:* Although intravenous administration of iron dextran, iron gluconate and iron sucrose is associated with laboratory evidence of oxidative stress in dialysis patients, the changes are modest, transient, and generally of a magnitude similar to that of the hemodialysis procedure itself. Although use of intravenous iron in the

hemodialysis patient population is extensive, there is no evidence that oxidative stress associated with acute administration of colloidal iron carbohydrates contributes to mortality or morbidity.[12] Specifically, there is no information linking intravenous-iron-related oxidative stress and dilated cardiomyopathy.

In addition, **Non-Clinical Pharmacologist consultant, Dr. Louis Grosso, PhD, DABT** provided an independent assessment of the non-clinical safety studies with iron sucrose and FCM specifically focusing on the histopathological examinations of the heart of treated rats and dogs. In addition to the overall study results, individual animal data from each study was reviewed. Dr. Grosso concluded that:

> *"The results of histological examinations in (iron replete) rats and dogs administered iron sucrose or FCM intravenously, indicate no cardiac adverse effects occur (sic) following 13 or 26 weeks of treatment with each drug respectively. The only finding was slight to moderate brown pigment (iron) deposition in macrophages of the heart. This finding would be expected in normal animals receiving relatively high doses of iron for 13 or 26 weeks. Brown pigment deposition was only observed in macrophages in heart and not observed in myocardial tissue from rats or dogs receiving iron sucrose or FCM."*

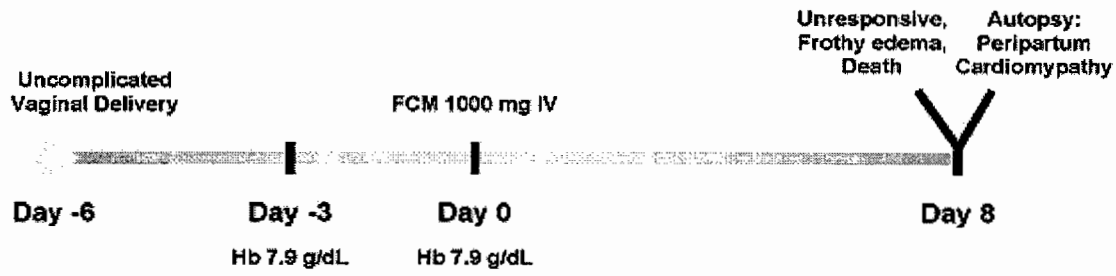
The chronic toxicity doses utilized were significantly higher (up to a total of 780 mg Fe/kg) than the 10 mg/kg Fe single dose received by this subject.

Finally, in the 3 days between screening and baseline, the subject gained 1.3 kg (90.9 kg to 92.2 kg). Weight gain is distinctly unusual during the early postpartum period: rather, a vigorous diuresis generally ensues after parturition, manifested by progressive weight loss over the first 2-4 weeks after delivery. This patient also reported one of the lowest scores (18.8) recorded for the vitality component of the SF-36 quality of life assessment. Vitality scores are in answer to the following questions: "Did you feel full of life?, Did you have a lot of energy?, Did you feel worn out?, and Did you feel tired?". Although the subject was reportedly asymptomatic and showed a normal physical exam at the time of enrollment, the weight gain and low vitality score are consistent with baseline, early onset of PPCM.

Summary Representing All Expert Reviews of Case 1 RCT

Case 1 RCT is a 27-year-old African American female with postpartum anemia, multiparity, and obesity. She had an uncomplicated vaginal delivery on [redacted]. This was her 4th delivery. On the [redacted], her hemoglobin was 7.9g/dL. She received FCM 1000mg on the [redacted] On the [redacted]d, she was found at home to be unresponsive with frothy edema. Attempts at resuscitation were unsuccessful and the patient *died from peripartum cardiomyopathy*. Autopsy confirmed a non-inflammatory, non-ischemic dilated cardiomyopathy consistent with peripartum disease. This case was also reviewed by the cardiomyopathy expert Dr. Cooper and the pathologist expert Dr. Phillips. There is no known mechanism that would link intravenous iron to peripartum cardiomyopathy. The subject had 3 major risk factors for peripartum cardiomyopathy. The death was judged unrelated to FCM by Investigator, clinical pharmacologist, and nephrologist/iron expert. The death was judged unrelated to toxic drug effect by the expert cardiologist and pathologist. Reviewers commented that they could not exclude cocaine or amphetamine use as a possible etiology. The death was judged unrelated to known intravenous iron adverse events such as anaphylaxis and hypotension. The death was also deemed unrelated to other study deaths, to non-fatal study adverse events, to low serum phosphate and to preclinical toxicology. A schematic of the subject's study timecourse is presented in **Figure 1**.

Figure 1. Schematic of Case 1 RCT



3.0 DEATHS IN FCM SUBJECTS IN OTHER RANDOMIZED CONTROLLED TRIALS

Indication/ Study/ID/ Country	Investigator Assessment of Cause of Death	External, Independent Experts Assessments of Probable Cause of Death	Age/ Sex/ Race	Last dose of FCM -mg	Time since last dose -days
Inflammatory Bowel Disease/ CL-08 Case 2 RCT/ Bulgaria	**Cardiac arrest, witnessed death**	• *Current illnesses:* ulcerative colitis, symptomatic aortic stenosis, mitral regurgitation, obesity • *Past Hx:* probable myocardial ischemia/angina • *Cause of death:* cardiac arrest in association with severe anemia (hemoglobin 4.8 g/dL one day prior to death) • *Pathogenesis:* Ischemia secondary to life threatening anemia in the setting of underlying valvular & ischemic heart disease • *Link to use of any iron agent, including FCM*: none • *Link to other trial deaths*: High co-morbidity	56/ M/ C	1,000	1 (26 hrs)
Hemodialysis dependent CKD/ CL-15/ Case 3 RCT/ Bulgaria	**Acute anterior myocardial infarction, documented in hospital**	• *Current Illnesses*: HD-CKD, diabetes x 14 years, diabetic nephropathy, retinopathy & neuropathy, HTN Grade III, chronic pyelonephritis. • *Cause of death:* documented acute extensive anterior myocardial infarction • *Pathogenesis*: acute blood loss (hemoglobin drop of 3.2g/dL 11.3→7.8 from 2 sources) resulting in a rapidly worsening anemia in the setting of presumed underlying CAD; suffered AMI, hospitalized with ST segment elevation x 4 d, tx'd without –lytics or angioplasty, arrested & died. 100-fold higher annual cardiovascular mortality rate than age matched population[13] • *Link to use of any iron agent, including FCM:* none • *Link to other trial deaths:* high co-morbidity	58/ M/ C	200	9 (AMI 4 days after first & only dose)
Non-dialysis dependent CKD/ VIT-04/ Case 4 RCT/ Australia	Multiple trauma s/p motor vehicle accident	• *Current Illnesses*: CKD, recurrent UTI, PVD, PUD, HTN, • *Past Hx*: s/p ruptured abdominal aortic • *Cause of death:* Trauma • *Pathogenesis:* Motor vehicle accident with no myocardial infarction or pulmonary embolism on autopsy • *Link to use of any iron agent, including FCM:* none • *Link to other trial deaths:* high co-morbidity	76/ M/ C	500	15
Non-dialysis dependent CKD/ VIT-04 Case 5 RCT/ US	Urosepsis with pneumonia, after being placed into hospice care	• *Current Illnesses*: CKD, CAD, HTN, atrial fibrillation, prostate cancer refractory to tx with hormone ablation (being treated with Casodex for advanced prostate cancer) • *Past Hx:* AMI, pneumonia • *Cause of death:* suffered fatal urosepsis secondary to bladder outlet obstruction • *Pathogenesis:* UTI complicated by bladder outlet obstruction 2^0 to prostate CA with pelvic radiation, in an elderly man with CAD. Course likely altered by family decision to not pursue aggressive treatment of Urosepsis when patient placed in hospice care. • *Link to use of any iron agent, including FCM*: none • *Link to other trial deaths:* high co-morbidity	85/ M/ C	1,000	35

Bold= cases of probably cardiac etiology.

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3.1 Case 2 RCT

Study Number: CL-08
Event: Cardiac arrest

This 56-year-old Caucasian male with iron deficiency associated with ulcerative colitis was consented on [redacted] His medical history is significant for valvular heart disease with aortic valve stenosis and regurgitation and mitral insufficiency (onset prior to March 2003), obesity (270.6 pounds, 67 inches) and ulcerative colitis (since 2003). The subject was hospitalized for 5 days in [redacted] for exertional dyspnea, fatigue and anemia. Electrocardiogram (ECG) showed possible myocardial ischemia. In [redacted] the subject was hospitalized 5 weeks for chest pain with exertion, fatigue, exhaustion and anemia. Both hospitalizations documented the history of aortic stenosis, mitral insufficiency and abnormal cardiovascular examinations consistent with his valvular heart disease. The patient received intravenous iron sucrose for his iron deficiency anemia during both hospitalizations.

The physical examination prior to study medication administration on [redacted] was remarkable for obesity and a systolic murmur in the 2nd right intercostal aortic space and 3rd left intercostal space. The ECG revealed a complete right bundle branch block. His average hemoglobin during the screening phase of the study was 5.45 g/dL with a TSAT of 2% and serum ferritin of 14 mcg/L. The patient's iron deficiency was calculated to be 2,274 mg.

The patient received his first and only dose of FCM 1000mg on [redacted]. Hemoglobin obtained immediately pre-dosing with FCM was 4.8 g/dL. His blood pressure on the day of dosing was 110/70 mmHg sitting and pulse 76 bpm. On [redacted] (study day 1, 26 hours after FCM dose) he experienced a sudden cardiac arrest, observed, at work. Resuscitation measures were initiated in the ambulance. At time of arrival to the hospital, the patient had no detectible heart activity and therefore an ECG was not performed. No autopsy was performed.

The Investigator considers the death unrelated to study drug and related to underlying cardiac disease.

3.1.1 Sponsor Commentary

Key data for Case 2 RCT are summarized in **Table 9**. In short, the subject was an obese 56-year-old male with known heart disease who suffered sudden death in association with profound iron deficiency anemia associated with ulcerative colitis. The likely cause of death was cardiac, as judged by the Investigator. The hemoglobin of 4.8 g/dL obtained on the day prior to death would have been considered life-threatening if found in the absence of cardiac disease. When coupled with aortic stenosis, mitral insufficiency and a suspiciously low blood pressure (100/60 to 110/70 mmHg), the anemia likely precipitated an ischemic ventricular arrhythmia.

No etiology potentially related to administration of either FCM or any class of intravenous iron agent is compatible with this patient's arrest and death. In particular, the timing of the death, 26 hours after administration of FCM, is too late to consider anaphylaxis and too early to consider either hypophosphatemia or a rapid increase in hemoglobin. As demonstrated in postpartum subjects in the VIT-06 safety trial, the observed phosphate decline during the 24 hour post-dosing period following 1,000 mg of FCM (the dose this subject received) was only 0.37 mg/dL (95% CI

-0.57 to -0.18). In the pharmacokinetic/pharmacodynamic study CL-02, no significant changes in hemoglobin occurred 1 day following dosing with 1,000 mg of FCM.

Table 9. Chronology of Dosing and Selected Data for Case 2 RCT

Study Subject	Age/ Sex/ Race	Date	Time	FCM Dose (mg)	B/P Sys/Dia (mmHg)	Blood Chemistry PO4 (mg/dL)	Na (mEq/L)	K (mEq/L)	Ca (mg/dL)	Hgb (g/dL)	Adverse Event Preferred Term	Stop Date (RxEday)
CL-08												
Case 2 RCT	56/M/C		NR		140/80 Sit							
			08:15			NC	131	4.9	8.64			
			08:00							5.5		
			08:00							5.4		
			NR		110/70 Sit							
			07:30			NC	138	4.6	9.04	4.8		
			08:00	1,000								
			08:20		100/60 Sit							
			08:45		105/70 Sit							
			10:00								Cardiac arrest	

Sys = systolic, Dia = diastolic, PO4 = phosphate, Na = sodium, K = potassium, Ca = calcium, Hgb = hemoglobin, RxEday = days since final dose of study drug, M = male, F = female, B = Black, C = Caucasian, NC = not collected, NR = not reported, Sit = sitting, Sup = supine, Std = standing

3.1.2 Independent Expert Review

Independent Clinical Pharmacology Safety Expert Dr. Judith Jones, MD, PhD and Staff, Degge Group

An initial review and an intensive re-review of this case with a focus on cardiovascular features was performed and concluded:

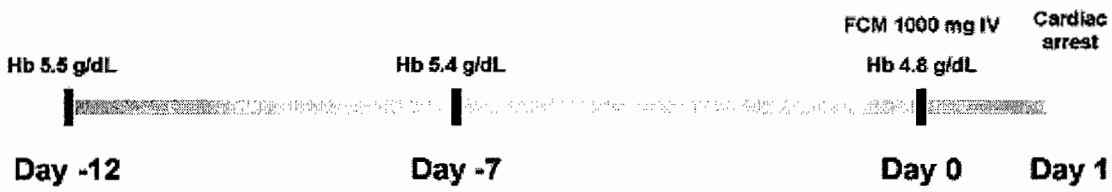
"This 56-year-old very obese male had a number of factors predisposing to his sudden death. These included his very severe anemia, treated the day prior, his aortic stenosis (known to be associated with sudden death), and his documented history of hospitalizations for cardiac ischemia, which were also associated with his recurrent anemia. Further, his right bundle branch block, likely associated with his valvular disease is similar to congenital syndromes that are also associated with sudden death. Although the temporal proximity to his FCM injection is of concern, there is little evidence of any particular mechanism that would explain its role in this death."

Summary Representing All Expert Reviews of Case 2 RCT

Case 2 RCT is a 56-year-old obese Bulgarian male (123 kg) with ulcerative colitis, aortic stenosis, mitral regurgitation and recent angina. On , his hemoglobin was 5.5g/dL and on repeated testing on the was 5.4g/dL. Seven days later, on the day FCM was administered, the hemoglobin was 4.8g/dL. He suffered cardiac arrest, observed, at work the following day. In this patient, the combination of severe anemia (hemoglobin 4.8g/dL) with aortic stenosis and mitral regurgitation precipitated sudden death. Most likely, his sudden death was related to myocardial ischemia in the setting of aortic stenosis and pre-existing angina. Had the patient been cared for in the United States, he would have been hospitalized for acute RBC transfusion after the first hemoglobin was observed. The death was judged unrelated to FCM by Investigator,

clinical pharmacologist, and nephrologist/iron expert. The death was judged unrelated to known intravenous iron adverse events such as anaphylaxis and hypotension. The death was also deemed unrelated to other study deaths, to non-fatal study adverse events, to low serum phosphate and to preclinical toxicology. A schematic of the subject's study timecourse is presented in Figure 2.

Figure 2. Schematic of Case 2 RCT



3.2 Case 3 RCT

Study Number: CL-15
Event: Myocardial infarction

This 58-year-old male patient with anemia of ESRD was consented on [redacted] His medical history is significant for non-insulin-dependent diabetes mellitus, diabetic retinopathy, allergic rhinitis, hypertension, diabetic neuropathy, and chronic pyelonephritis. The patient had AV-fistula surgery in [redacted] and permanent catheter implant in [redacted] The patient started hemodialysis in [redacted] with 3 sessions per week.

The patient's hemoglobin during his screening visit on [redacted], 2004 was 11.0 g/dL with a TSAT of 14% and serum ferritin of 17 mcg/L. On [redacted] his hemoglobin was 9.3 g/dL. The patient's iron deficiency was calculated to be 1,162 mg.

The patient received his first and only dose of FCM 200 mg on [redacted] and had 1 session of hemodialysis. On the same day (study day 0), the patient experienced clotting in blood lines and filter complicated by subsequent loss of blood, at the end of hemodialysis. The event resolved with sequelae and the patient was discontinued from the trial.

On [redacted] (study day 4) the patient presented with severe chest pain, nausea, and sweating. A diagnosis of acute myocardial infarction with ST segment elevation was made using ECG, clinical and enzyme data (CPK 778-173, CPK-MB 75-22). His hemoglobin was 7.8 g/dL. His hospital course was complicated by congestive heart failure. The patient was treated with IV Perlinganit (vasodilator), IV heparin, IV Corvitol (Metoprolol), and Furanthril (diuretic) and IV fentanyl.

On [redacted] (study day 9) he experienced a cardiac arrest during his dialysis session, and was given Dopamine, adrenalin and atropine. Resuscitation efforts did not stabilize his vital signs, and the patient died. No autopsy was performed.

The Investigator considers the serious adverse event (myocardial infarction with subsequent death) to be unrelated to study drug.

3.2.1 Sponsor Commentary

Key data for Case 3 RCT are summarized in **Table 10**. In short, this is a 58-year-old man with hemodialysis-dependent CKD, diabetes, hypertension and heart disease who suffered an acute anterior myocardial infarction with congestive heart failure and death. Acutely worsening anemia first identified prior to treatment with FCM (hemoglobin decrease 3.2 g/dL in 12 days, 11 to 7.8 g/dL), complicated by subsequent loss of blood due to clotting of the extracorporeal circuit (blood tubing and dialyzer) on the same day may have played a role in precipitating the acute event. Annual cardiovascular mortality among white males 55-64 years of age undergoing chronic dialysis is nearly 100-fold higher than that seen in the age-matched general population.[13] Cardiac events are the leading cause of death among dialysis patients in the United States.[13]

No etiology potentially related to administration of either FCM or any class of intravenous iron agent is compatible with this patient's myocardial infarction and death. In particular, the timing of the acute myocardial infarction, 4 days after administration of FCM, is too late to consider anaphylaxis or labile iron reaction (neither of which has been seen after FCM administration).

The phosphate decrease seen in FCM treated hemodialysis subjects is modest with no subjects reaching a nadir phosphate <2 mg/dL. The event was also too early to consider hypophosphatemia, which, in any case, has not been described in association with acute myocardial infarction. A rapid increase in hemoglobin is effectively excluded by evidence of a fall in hemoglobin level that began in the week prior to FCM administration and continued through hospitalization. Finally, this patient received only a single 200 mg dose of FCM. The conclusion that this death was not related to study drug administration is well-supported by the available evidence.

Table 10. Chronology of Dosing and Selected Data for Case 3 RCT

Study Subject	Age/ Sex/ Race	Date	Time	FCM Dose (mg)	B/P Sys/Dia (mmHg)	Blood Chemistry PO4 (mg/dL)	Na (mEq/L)	K (mEq/L)	Ca (mg/dL)	Hgb (g/dL)	Adverse Event Preferred Term	Stop Date (RxEday)
CL-015												
Case 3 RCT	58/M/C		NR		160/80 Sit							
			08:30			NC	136	5.3	10.6	11.0		
			08:50		160/90 Sit							
			08:55			NC	138	4.0	8.64	9.3		
			10:05	200							Medical device complication	
			NR								Nasopharyngitis	
			NR								Myocardial infarction	
			NR				136	4.4		7.8		
			10:45								Muscle cramp	

Sys = systolic, Dia = diastolic, PO4 = phosphate, Na = sodium, K = potassium, Ca = calcium, Hgb = hemoglobin, RxEday = days since final dose of study drug, M = male, F = female, B = Black, C = Caucasian, NC = not collected, NR = not reported, Sit = sitting, Sup = supine, Std = standing

3.2.2 Independent Expert Review

Independent Clinical Pharmacology Safety Expert Dr. Judith Jones, MD, PhD and Staff, Degge Group

An initial review and an intensive re-review of this case with a focus on cardiovascular features was performed and concluded:

"This 58-year-old male with longstanding diabetes and more recent complications, including diabetic nephropathy requiring dialysis from on, experienced an acute myocardial infarction 4 days after receiving 1 dose of FCM. Records are very sketchy and incomplete. During hospitalization, the patient was given intravenous nitrates and metoprolol and diuretics. On the fifth day after hospitalization, he experienced bradycardia (per ECG) and bradysystolic arrest and died. Although this is one possible outcome of an acute myocardial infarction complicated by congestive heart failure, the bradyarrhythmia would also be consistent with a direct effect of the metoprolol as the cause of his demise."

Dr. Leslie T. Cooper (Professor of Medicine, Mayo Clinic):

Case 3 RCT was a 58-year-old man (at time of consent on with a history of type 2, insulin dependent diabetes, chronic renal failure requiring dialysis since

hypertension, and anemia. He had no known history of coronary artery disease and an EKG dated [redacted] revealed only sinus rhythm at 70 bpm with no acute ischemic changes. He received the first and only dose of FCM 200 mg in a clinical trial on [redacted] and had no significant acute changes in heart rate or blood pressure during the 120 minute monitoring period following study drug administration.

The subject was admitted to the [redacted] with chest pain ("praecordial oppression") which started on [redacted] at 20:00 the pain became more severe and radiated to both hands, and the patient developed "nausea and sweating." The physical examination and report of the chest radiograph suggested congestive heart failure with pulmonary edema. He also has a holosystolic murmur suggesting of mitral regurgitation, which was previously not documented. The EKG dated [redacted] revealed ST segment elevation in leads V1 through V6, I and aVL consistent with an anterolateral myocardial infarction. He was treated with heparin, beta blocker, ("metoprolom"), intravenous nitrates, telmisartan (Micardis), and dipyridamole. He did not undergo coronary angiography or have an attempt at coronary revascularization. No assessment of left ventricular function or cardiac monitoring is recorded in the source documents or case report forms. On [redacted] the subject expired following a bradycardic asystolic cardiac arrest. An autopsy was not performed.

Discussion: The first question is whether the subject's medical treatment for acute myocardial infarction met the 2004 standards of care. The first step in the management of the patient with an ST elevation myocardial infarction (STEMI) is prompt recognition, since the beneficial effects of early therapy with reperfusion are greatest when performed early after the onset of symptoms. In this subject's case the diagnosis of an STEMI was confirmed by the ECG and serum CK-MB enzyme elevation; however, at the time of presentation more than 24 hours had elapsed since the onset of chest pain. Therefore, he fell outside the time window where thrombolytic therapy and percutaneous coronary intervention are proven to be of benefit. However, in cases where ischemia recurs, revascularization may be indicated. In this case, there is no documentation of serial cardiac enzymes or symptoms after admission to determine whether he had recurrent ischemia.

The 2004 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on STEMI included a number of recommendations, some of which were met and some of which were not in this case.[15] According to the ACC/AHA guideline, patients with STEMI should receive antiplatelet therapy, antithrombotic therapy, beta-blockade, and angiotensin converting enzyme inhibition. The subject in this case did receive these therapies.

However, the CRFs and source documents do not document other standard tests and assessments. Findings indicative of increased risk for future coronary events and mortality include left ventricular dysfunction as assessed by noninvasive tests and recurrent ischemia. Assessment of resting left ventricular function in patients with acute MI was given a class I recommendation by the 2004 ACC/AHA STEMI guidelines. Furthermore, in this case the subject had an apparently new mitral regurgitation murmur, which may have resulted from a ruptured papillary muscle. An echocardiogram was indicated to determine the mechanism of mitral regurgitation as well as to assess left ventricular function. Tests of left ventricular function and cardiac monitoring were not documented in the CRFs or source documents.

This subject had high risk features including heart failure and an anterior MI. Patients at high risk are usually considered to require an aggressive management strategy in addition to standard medical management. Interhospital transfer to a facility with revascularization capabilities is

recommended for such patients.[15] *The source documents contain no record of consideration of revascularization.*

The ACC/AHA guidelines also gave a class I recommendation to the administration of an aldosterone receptor antagonist to all STEMI patients who are already receiving an ACE inhibitor, have either symptomatic HF or diabetes, and have an LVEF ≤40 percent. The subject met the clinical criteria and the LVEF was most likely less than 40%, but he did not receive an aldosterone receptor antagonist.

Initial intensive statin therapy, rather than gradual dose titration upward, is also recommended because of the suggestion of benefit in the PROVE IT-TIMI 22 trial.[16] *In this case no assessment of lipids or statin therapy was documented.*

Randomized trials have demonstrated that both diabetics and nondiabetics who have had an acute MI or are critically ill benefit from tight blood glucose control. No record of ongoing blood glucose monitoring was available in the CRFs or source documents. The 2004 ACC/AHA guidelines gave a class I recommendation to the use of an insulin infusion to normalize blood glucose in patients with an STEMI and a complicated course, regardless of whether they have a diagnosis of diabetes mellitus. There is no documentation of this treatment in this case.

In this case the subject received dilitazem (90mg BID up to [redacted]), which may have been harmful. No calcium channel blocker has been shown to reduce mortality in acute STEMI, and in certain patients they may be harmful, such as those with evidence of heart failure and/or left ventricular dysfunction.[17] *This drug was appropriately stopped, but residual negative inotropic effects may have contributed to heart failure in the setting of likely severe left ventricular dysfunction.*

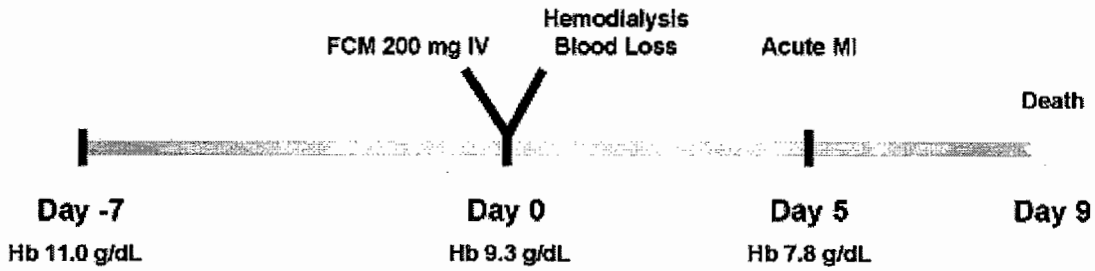
The second question is whether optimal medical care would have impacted the likelihood of death in this case. In my estimation, the subject would have had a greater likelihood of survival had he received optimal care as outlined in the 2004 AHA/ACC STEMI guideline. This opinion is based on the randomized trial data cited above which were published prior to the subject's treatment in 2004.

Summary Representing All Expert Reviews of Case 3 RCT

Case 3 RCT is a 58-year-old Bulgarian male hemodialysis patient with diabetes and hypertension. On the day when he received his only single FCM dose of 200 mg, his hemoglobin was 9.3 g/dL - a 3 g/dL (or 6 point hematocrit) drop from 11.3 g/dL. This is equivalent to over 1000cc loss of whole blood. Subsequently, he lost another 250cc blood loss from clotted dialyzer. He was hospitalized on [redacted] for signs and symptoms of acute MI (chest pain, ST elevations, Q wave changes). He was not transfused, was not revascularized, was not administered lytic therapy, and was not assessed for left ventricular function or a new mitral regurgitant heart murmur. His care in Bulgaria fell short of that expected in the US. Had the patient been treated in the U.S., the standard of care would have included follow-up hemoglobin on the next dialysis treatment after loss of a dialyzer-tubing set, transfusion of RBCs for severe anemia in the setting of acute myocardial ischemia, and evaluation of LV function, at the least. His pre-existing risk factors of hemodialysis with end stage renal disease, diabetes, and hypertension contributed to his high cardiovascular risk. The death was judged unrelated to FCM by Investigator, clinical pharmacologist, and nephrologist/iron expert. The death was judged unrelated to known intravenous iron adverse events such as anaphylaxis and hypotension. The death was also deemed unrelated to other study deaths, to non-fatal study adverse events, to low serum

phosphate and to preclinical toxicology. A schematic of the subject's study timecourse is presented in Figure 3.

Figure 3. Schematic of Case 3 RCT



3.3 Case 4 RCT

Study Number: VIT-04
Event: Multiple Trauma due to Motor Vehicle Accident

This 76-year-old male with ND-CKD and anemia was randomized to FCM on [redacted] His medical history is also significant for recurrent UTI, peptic ulcer disease, hypertension, and a ruptured abdominal aortic aneurysm in [redacted]. He received his first dose of FCM (1000 mg) intravenous on study day 0. His second dose (500 mg) was given on study day 20. His third and final dose (500 mg) was given on study day 30. His baseline hemoglobin was 10.3 g/dL. On day 42 of the study, his hemoglobin was 11.9 g/dL. On [redacted] (fourteen days after his last dose) he received multiple injuries in a motor vehicle accident. He died of multiple injuries on [redacted] (study day 45). His wife also died at the scene of the accident from multiple injuries.

Autopsy report indicates that he was the driver of the vehicle which appeared to contravene a stop sign and collided with another vehicle. He then collided with a gate and fence coming to rest in a ditch. He had extensive external and internal signs of blunt trauma to the head, neck, chest, abdomen and all extremities. He had multiple rib fractures, bilateral lung contusions, dissection of the thoracic aorta and there was blood in the chest and abdominal cavities. He had a torn mesentery. A splenectomy had been performed at the hospital. He had fractures of the pelvis, mandible, and right scapula. There was no evidence of an acute myocardial infarction (no thromboembolic occlusion) or lung infarction. Toxicological analysis showed the presence of a therapeutic list of drugs. No alcohol was noted. The autopsy report stated that the cause of death was therefore due to multiple injuries.

The Investigator considers this serious adverse event (multiple trauma due to MVA) unrelated to study drug.

3.3.1 Sponsor Commentary

Key data for Case 4 RCT are summarized in **Table 11**. In short, this was a 76-year-old man with anemia associated with chronic kidney disease, not requiring dialysis who received his last dose of FCM fifteen (15) days prior to his death. The subject died 1 day following an intersection motor vehicle accident (MVA) involving a second automobile from massive and extensive blunt trauma. The coroner's report clearly documents the extensive blunt trauma incurred due to the MVA supported by immediate passenger death at the trauma scene. The external and internal autopsy findings are consistent. For example there was extensive external chest and abdominal trauma consistent with the documented multiple rib fractures, lung contusions, dissection of the thoracic aortic aneurysm, splenic and abdominal hemorrhage. The autopsy revealed no evidence of an acute myocardial infarction or pulmonary embolism. The MVA occurred in Australia and no further hospital information is available.

Table 11. Chronology of Dosing and Selected Data for Case 4 RCT

Study Subject	Age/ Sex/ Race	Date	Time	FCM Dose (mg)	B/P Sys/Dia (mmHg)	Blood Chemistry PO4 (mg/dL)	Na (mEq/L)	K (mEq/L)	Ca (mg/dL)	Hgb (g/dL)	Adverse Event Preferred Term	Stop Date (RxEday)
VIT-04												
Case 4 RCT	76/M/C		12:05			3.3	139	4.7	9.1	10.2		
			11:30			3.5	139	5.1	9.3	10.4		
					124/78 Sit							
			11:04		103/68 Std							
			11:39	1,000								
					144/85 Sit							
			12:00		149/79 Std							
					141/81 Sit							
			12:30		138/83 Std							
					136/81 Sit							
			13:00		146/80 Std							
			11:26			2.4	141	4.6	9.2	10.3		
					134/75 Sit							
			12:03		135/75 Std							
			12:34	500								
					134/77 Sit							
			12:49		147/83 Std							
			13:20		146/81 Sit							
					147/71 Std							
					150/83 Sit							
			13:50		148/89 Std							
			11:20			2.4	142	4.4	8.7	10.8		
					140/85 Sit							
			09:00		136/79 Std							
			09:19	500								
					146/77 Sit							
			09:36		151/86 Std							
					136/78 Sit							
			10:10		128/80 Std							
					142/86 Sit							
			10:36		161/89 Std							
			11:26			NR	NR	NR	NR	11.9		
			NR								Road traffic accident	
			NR								Polytraumatism	

Sys=systolic, Dia=diastolic, PO4=phosphate, Na=sodium, K=potassium, Ca=calcium, Hgb=hemoglobin,
RxEday = days since final dose of study drug, M=male, F=female, B=Black, C=Caucasian, NC=not collected, NR=not reported,
Sit=sitting, Sup=supine, Std=standing

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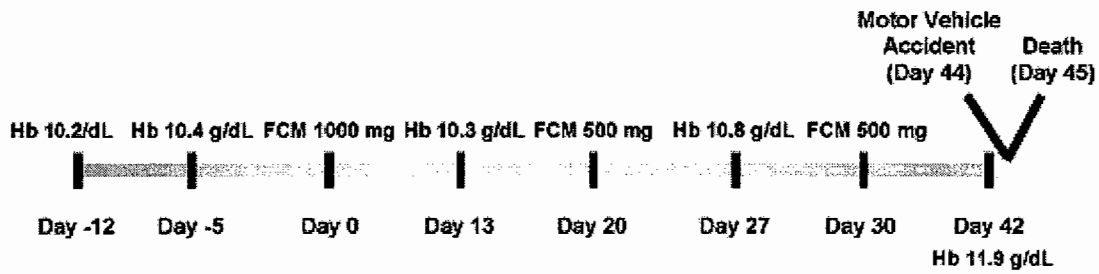
Summary Representing All Expert Reviews of Case 4 RCT

Case 4 RCT is a 76-year-old male with chronic kidney disease, recurrent UTI, peptic ulcer disease, hypertension, status post ruptured abdominal aortic aneurysm in [redacted] He suffered death from a fatal motor vehicle accident. The death was judged to be due to multiple injuries by the coroner following a full autopsy showing no myocardial infarction or pulmonary embolus. The death was judged unrelated to FCM by Investigator, clinical pharmacologist, and nephrologist/iron expert. The death was judged unrelated to known intravenous iron adverse events such as anaphylaxis and hypotension. The death was also deemed unrelated to other study deaths, to non-fatal study adverse events, to low serum phosphate and to preclinical toxicology. A schematic of the subject's study timecourse is presented in **Figure 4**.

Figure 4. Schematic of Case 4 RCT



3.4 Case 5 RCT

Study Number: VIT-04
Event: Urosepsis

This 85-year-old chronically ill male was randomized to FCM on [redacted] His past medical history is significant for ND-CKD, anemia, coronary artery disease (CAD), myocardial infarction, hypertension, atrial fibrillation, pneumonia, prostate cancer, and bladder outlet obstruction. He had at least 2 previous admissions for urinary tract infection secondary to urinary retention. The urinary retention was secondary to previous radiation therapy for prostate cancer. He had a longstanding history of prostate cancer which was under control with hormonal treatment. However, the prostate cancer reactivated with elevating PSA and was resistant to hormonal control. The patient had been started on Casadex for advanced prostate cancer prior to enrollment in the study.

He received his only dose of FCM (1000 mg) intravenous on study day 1. He was admitted to the hospital on [redacted] (32 days after receiving FCM) with several days of decreasing oral intake, weakness, lethargy, fever and most recently labored respirations. Upon arrival to the ED his temperature was 102.3^0, irregular heart rate of 140, BP 118/73 and respiratory rate of 30. EKG revealed atrial fibrillation with rapid ventricular response, rate 129 beats per minute, non specific ST-T wave abnormality. Chest x-ray showed a LLL infiltrate. Retroperitoneal ultrasound showed bilateral moderate hydronephrosis with bladder outlet obstruction, chronic renal disease, mild ascites, and right pleural effusion. Urine and blood cultures grew methicillin resistant staph aureus (MRSA). He was treated with intravenous fluids and antibiotics. The patient's condition continued to deteriorate with dropping blood pressures. The patient had a comprehensive living will and advanced directive. In accordance with this, the patient and family decided that they did not want any further treatment, dialysis, or medications to support his blood pressure, and chose to provide only comfort measures. He was discharged to hospice care on study day 35 with diagnoses of urosepsis and pneumonia. He died [redacted] (study day 35) in hospice after withdrawal of therapy.

He was discontinued from the study on study day 33 for intervention (increase of erythropoietin dose).

The Investigator considers this serious adverse event (urosepsis) unrelated to study drug.

3.4.1 Sponsor Commentary

Key data for Case 5 RCT are summarized in **Table 12**. In short, this was an 85-year-old man with bladder outlet obstruction, advanced prostate cancer unresponsive to radiation and hormonal therapy, chronic kidney disease and a history of recurrent urinary tract infections. He suffered urosepsis with methicillin resistant staphylococcus aureus (MRSA) bacteremia and pneumonia and died the day after resuscitative measures were withdrawn or withheld. The presentation, clinical course and death are fully explained by the patient's pre-existing co-morbid conditions. In an elderly male with urinary tract infection, the presence of bladder outlet renders urinary sterilization difficult, recurrent infections expected, presentation with urosepsis more likely, and, if urosepsis arises, death likely. The occurrence of the infection 33 days after FCM administration effectively precludes either study drug or altered iron status as a potential contributing factor. Pharmacokinetic studies (CL-02) confirm that FCM is undetectable in

plasma within a week after administration. Moreover, the study patient showed a normal transferrin saturation 2 days prior to admission (31%), effectively excluding supersaturation of transferrin as a stimulus to bacterial growth. The subject's ferritin, drawn simultaneously, was 568 ng/mL, in keeping with the patient's chronic kidney disease and carcinoma. Finally, there is no evidence that FCM specifically or intravenous iron agents of any class increase the risk of infection, including that by Staphylococcus.[18,19]

Pre-treatment hemoglobin was 10.2 g/dL and phosphate was 3.9 mg/dL. Hemoglobin on the day of the urosepsis serious adverse event ( ) was 10.4 g/dL. Hemoglobin was 8.1 g/dL and serum phosphate was 2.6 mg/dL on the day of death ((35 days after last dose of FCM).

Available evidence in this patient is more than sufficient to support the Investigator's judgment that this infection and death were unrelated to study drug.

Table 12. Chronology of Dosing and Selected Data for Case 5 RCT

Study Subject	Age/ Sex/ Race	Date	Time	FCM Dose (mg)	B/P Sys/Dia (mmHg)	Blood Chemistry PO4 (mg/dL)	Na (mEq/L)	K (mEq/L)	Ca (mg/dL)	Hgb (g/dL)	Adverse Event Preferred Term	Stop Date or Time (RxEday)
VIT-04												
Case 5 RCT	85/M/C					3.9	137	3.7	7.9	10.2		
						3.8	139	3.4	8.1	10.2		
											Injection site extravasation	
			14:15		154/62 Sit							
			14:25	1,000								
			14:45		148/68 Sit							
			15:15		126/52 Sit							
			15:45		128/60 Sit							
			14:20		118/64 Sit	3.4	137	4.8	7.7	9.4		
			13:10		104/60	4.0	136	4.6	7.9	10.2		
			19:54		118/73	NC	141	4.3	7.7	10.4	Urosepsis	
			06:57			NC	NC	NC	NC	10.2		
			13:24			NC	131	3.9	7.4	8.7		
			06:08			2.6	128	4.5	7.4	8.1		

Sys = systolic, Dia = diastolic, PO4 = phosphate, Na = sodium, K = potassium, Ca = calcium, Hgb = hemoglobin, RxEday = days since final dose of study drug, M = male, F = female, B = Black, C = Caucasian, NC = not collected, NR = not reported, Sit = sitting, Sup = supine, Std = standing

Additional information was requested to document the details of the prostate cancer reoccurrence. Hospitalization records documented "adenocarcinoma of the prostate reactive with escalating PSA and refractory to treatment with hormone ablation." "Recently started on Casodex (bicalutamide; for advanced prostate cancer) for the same". Subject was on Casodex at the time of study entry. Additional references to the carcinoma being reactive were documented in the records. Patient had a living will and did not wish the use of artificial life support measures and was discharged to hospice care.

3.4.2 Independent Expert Review

Independent Clinical Pharmacology Safety Expert Dr. Judith Jones, MD, PhD and Staff, Degge Group

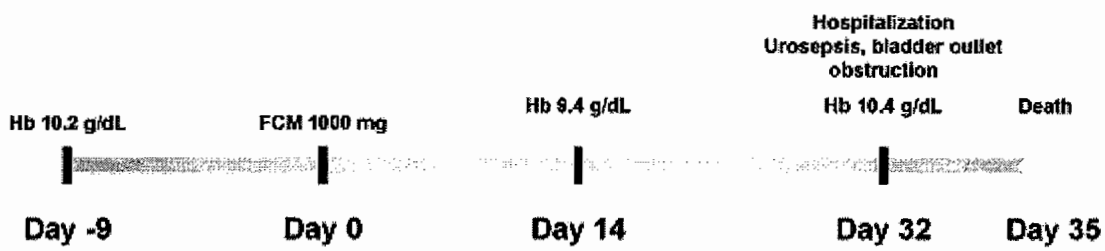
An initial review and an intensive re-review of this case with a focus on cardiovascular features was performed and concluded:

"This 85-year-old very chronically ill gentleman had many chronic disorders. The likely precipitating factor for his death was MRSA sepsis, which despite some response was accompanied by hypotension and a downhill course. By choice of the family, aggressive treatment was not pursued and he died in Hospice shortly after discharge. He had a history of coronary artery disease and upon hospital admission was in rapid atrial fibrillation with non-specific ST changes. Troponin was elevated upon admission but other enzymes were not elevated, inconsistent with MI diagnosis. Of note was that he was taking Provigil (modafinil) which is not indicated in individuals with cardiac disease. It is not clear that this had any contribution to the clinical picture here. There is no evidence to link his one injection of FCM to this death based upon the record review."

Summary Representing All Expert Reviews of Case 5 RCT

Case 5 RCT is an 85-year-old male with CKD Stage 4-5 with GFR <20, coronary artery disease, CHF, hypertension, atrial fibrillation, and prostate cancer refractory to radiotherapy and hormonal ablation, and acute MRSA urosepsis secondary to bladder outlet obstruction. He was hospitalized on [redacted] for urosepsis given bladder outlet obstruction. He was treated appropriately, but remained weak and poorly responsive and faced the possibility of chronic dialysis. His family invoked the patient's advanced directives and the patient *died after withdrawal of therapy and referral to Hospice care*. The death was judged unrelated to FCM by Investigator, clinical pharmacologist, and nephrologist/iron expert. The death was judged unrelated to known intravenous iron adverse events such as anaphylaxis and hypotension. The death was also deemed unrelated to other study deaths, to non-fatal study adverse events, to low serum phosphate and to preclinical toxicology. A schematic of the subject's study timecourse is presented in **Figure 5**.

Figure 5. Schematic of Case 5 RCT



4.0 DEATHS IN CONTROL PATIENTS IN RANDOMIZED CONTROLLED TRIALS

4.1 Overview of Deaths in Control Patients in Randomized Controlled Trials

Indication/ Study/ID/ Country	Investigator Assessment of Cause of Death	Major Pre-existing Conditions/Risk Factors Other than Anemia	Age/ Sex/ Race	Last dose of Iron Sucrose (mg)	Time since last dose (days)
Congestive Heart Failure/ CARS/ Case 1 Control RCT/ Russia	**Worsening Heart Failure**	• ND-CKD • CHF NYHA Class IV • HTN • Angina, MI x3, • atrial fibrillation • thromboembolus of the pulmonary artery	72/ F/ C	200	5

Bold= cases of probable cardiac etiology.

4.2 Case 1 Control Death in RCT

Study: CARS
Event: Worsening Heart Failure

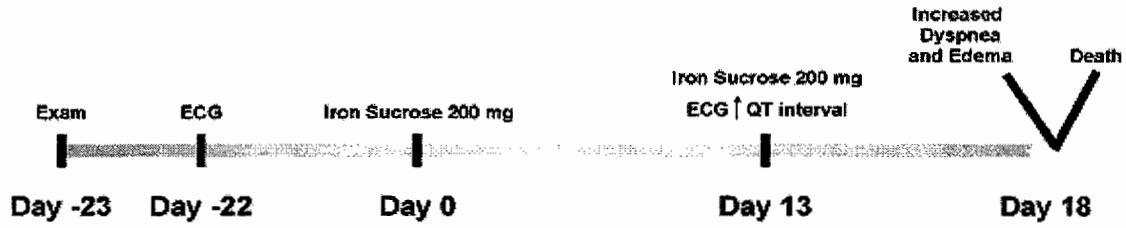
This 72-year-old female with chronic heart failure, renal failure and anemia was randomized on [redacted] Her medical history is significant for arterial hypertension, angina pectoris, myocardial infarction ([redacted]), thromboembolus of the pulmonary artery, atrial fibrillation, chronic pyelonephritis, peptic ulcer, heart failure, and renal failure (GFR 40.9 ml/min). Her physical exam on [redacted] demonstrated cardiomegaly, atrial fibrillation and 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 [redacted] 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 intravenous on study day 0. 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 study day 13. No adverse events were noted on this day of dosing. ECG done on [redacted] indicated an increase in the QT interval. Due to the increase in QT interval, her amiodarone treatment for arrhythmia was stopped. On study day 18, her family reported that she had increased dyspnea and edema. Her heart failure worsened and she died on [redacted] (study day 18). No autopsy was performed.

When the study blind was broken the study drug for this patient was confirmed to be iron sucrose.

The Investigator considers the serious adverse events (worsening heart failure) unrelated to study drug.

A schematic of the subject's study timecourse is presented in **Figure 6**.

Figure 6. Schematic of Case 1 Control in RCT



5.0 DEATHS IN FCM SUBJECTS IN UNCONTROLLED TRIALS

5.1 Overview of Deaths in FCM Patients in Uncontrolled Trials

Indication/ Study/ID/ Country	Investigator Assessment of Cause of Death	External, Independent Experts Assessments of Probable Cause of Death	Age/ Sex/ Race	Last dose of FCM -mg	Time since last dose -days
Hemodialysis dependent CKD/ VIT-53214/ Case 1 Uncontrolled/ Romania	**Possible Heart Failure, unwitnessed death**	• *Past Hx:* HD-CKD, poorly controlled HTN, ischemic & uremic cardiomyopathy, LVH, chronic CHF-NYHA Class III with recent hospitalization, atrial fibrillation, pericarditis & anemia (hemoglobin 6mg/dL) • *Cause of death:* probable cardiovascular cause • *Pathogenesis:* Chronic CHF 2^0 to ischemic & uremic cardiomyopathy in the setting of chronic HD, anemic HD pts hospitalized with CHF have a 50% annual mortality rate • *Link to use of any iron agent, including FCM*: none • *Link to other trial deaths:* high co-morbidity	54/ F/ C	100	19
Hemodialysis dependent CKD/ VIT-53214/ Case 2 Uncontrolled/ Lithuania	Respiratory insufficiency (with progressive SOB & hypoxia during 14 day hospitalization) due to infiltrating pulmonary TB	• *Past Hx:* HD-CKD, active pulmonary TB with multiple hospitalizations to Tb hospitals, CAD, COPD, chronic persistent hepatitis • *Cause of death*: respiratory failure secondary to tuberculous pneumonia • *Pathogenesis:* Active TB in the setting of chronic lung disease & chronic heart, liver and kidney disease, in a patient undergoing chronic hemodialysis • *Link to use of any iron agent, including FCM:* none • *Link to other trial deaths:* high co-morbidity	59/ F/ C	200	15
Iron Deficiency Anemia/ VIT-06/ Case 3 Uncontrolled/ US	Pneumonia, respiratory failure, sepsis-positive sputum & blood cultures	• *Past Hx:* recurrent infections, depression on multiple psychotropic meds, seizures, gastric bypass for morbid obesity • *Cause of death:* Septic shock and acute respiratory failure secondary to *Aeromonas* pneumonia/septicemia • *Pathogenesis: Aeromonas* pneumonia in a patient with chronic illness, recurrent infections, & use of broad spectrum antibiotics. Independent cardiologist confirmed no AMI or CHF. • *Link to use of any iron agent, including FCM*: none • *Link to other trial deaths:* high co-morbidity	48/ F/ C	1,000	27
Non-dialysis dependent CKD/ VIT-05/ Case 4 Uncontrolled/ US	Colonic (Sigmoid) Perforation, surgically verified, diverticulitis perforation on pathology report	• *Past Hx*: CKD, diverticulosis, diverticulitis, DM type II, CAD, HTN, & previous hepatic abscess, • *Cause of death:* Colonic rupture with abdominal sepsis • *Pathogenesis:* Diverticulosis complicated by chronic bleeding, recurrent penetration, and acute perforation with peritonitis in an elderly man with coronary artery disease, chronic kidney disease and rheumatoid arthritis • *Link to use of any iron agent, including FCM:* none • *Link to other trial deaths:* high co-morbidity	86/ M/ C	500	98
Non-dialysis dependent CKD/ VIT-05/ Case 5 Uncontrolled/ US	Anoxic encephalopathy, GI bleeding	• *Past Hx:* CKD, DM type II, HTN, hyperlipidemia, chronic edema, recurrent UTIs • *Cause of death:* Massive GI bleeding after exploratory laparotomy • *Pathogenesis:* Anatomic site not identified, but this post-menopausal female patient suffered chronic GI bleeding manifested by recurrent iron deficiency anemia prior to fatal episode of bleeding early after laparatomy • *Link to use of any iron agent, including FCM:* none • *Link to other trial deaths:* high co-morbidity	64/ F/ C	500	46

Bold=cases of probable cardiac etiology

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5.2 Case 1 Uncontrolled

Study Number: VIT-53214
Event: Cardiac failure acute

This 54-year-old female with CKD and anemia was consented on [redacted] Her medical history is significant for hypertension [redacted], oliguria [redacted]), and mixed ischemic and uremic cardiomyopathy [redacted], pericarditis ([redacted], glomerulonephritis, and congestive cardiac failure-NYHA II [redacted]). She started hemodialysis in [redacted] On [redacted], she was admitted to the hospital for 7 days in for treatment of congestive heart failure, NYHA III.

Baseline hemoglobin was 6.8 g/dL, TSAT 8% and ferritin 36 ng/ml. The patient's iron deficit was calculated to be 1,595 mg. She received her first dose of 200 mg of FCM on [redacted] and received 7 additional doses of 200 mg FCM during 7 hemodialysis sessions. The patient's eighth and last dose of FCM (100 mg) was administered on [redacted] (study day 16.). Electrocardiograms performed on [redacted] and again on study day 1, 14, and 28. were considered abnormal, but not clinically significant.

On [redacted] (study day 35; 19 days after last dose of FCM), the patient died at home. Her death was unobserved by medical practioners, and no autopsy was performed. The cause of death was listed as heart failure by the patient's family physician with preceding causes of atrial fibrillation, hypertensive disease and end stage chronic renal failure. A subsequent interview with the subject's family physician who completed the death certificate indicated that the patient did not demonstrate any progressive signs and symptoms of heart failure prior to death and they have no evidence regarding that her death was due to acute heart failure.

The Investigator considers this adverse event and death unrelated to study drug.

5.2.1 Sponsor Commentary

Key data for Case 1 Uncontrolled are summarized in **Table 13**. In short, she was a 54-year-old chronic hemodialysis patient with poorly controlled hypertension and substantial cardiac co-morbidity who showed evidence of severe iron deficiency anemia at baseline. Her death was suspected to be from acute congestive heart failure, which was unobserved by medical practitioners, and would be consistent with her previous history of ischemic and uremic cardiomyopathy with high-grade NHYA II functional deficits in a patient undergoing chronic hemodialysis.

The anemia responded briskly to iron replacement therapy reaching 10.1 g/dL, 8 days prior to death. Though a rapid increase in hemoglobin after administration of epoetin alfa has been associated with hypertensive encephalopathy or seizures in hemodialysis patients, in clinical trials worsening hypertension has not been seen among the anemic hemodialysis subjects treated with FCM or iron sucrose when erythropoiesis-stimulating agents are absent or are continued at a constant dose. Moreover, this patient showed no evidence of hypertensive encephalopathy or seizure; no evidence of worsening hypertension early after initiating iron therapy, despite an increase in hemoglobin exceeding 1.0 g/dL in 2 weeks; and, no evidence of worsening hypertension at the time of death. FCM data have shown that the incidence of serious adverse events was low and comparable to iron sucrose regardless of the maximum hemoglobin and rate of rise in hemoglobin during the study and that the serious adverse event rate was highest in the populations achieving the lowest maximum hemoglobin (<11 g/dL).

Hypophosphatemia may develop after rapid correction of anemia. Although phosphate levels were not measured in this trial or in this patient, evidence from the VIT-06 trial confirmed that the observed decrease in phosphate levels in hemodialysis subjects after administration of FCM is modest. Among 19 hemodialysis subjects in the VIT-06 safety study who received a single dose of FCM (15 mg/kg up to a maximum of 1,000 mg), 12 showed a modest decrease in serum phosphate level compared to baseline, but no subject given FCM experienced a nadir phosphate <2 mg/dL [CTCAE Grade 3].

It is unlikely that FCM administration played a contributing role in this subject's demise.

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Table 13. Chronology of Dosing and Selected Data for Case 1 Uncontrolled

Study Subject	Age/ Sex/ Race	Date	Time	FCM Dose (mg)	B/P Sys/Dia (mmHg)	Blood Chemistry PO4 (mg/dL)	Na (mEq/L)	K (mEq/L)	Ca (mg/dL)	Hgb (g/dL)	Adverse Event Preferred Term	Stop Date (RxEday)
VIT-53214												
Case 1 Unc	54/F/C		07:00			NC	NC	NC	NC	6.7		
			07:00			NC	NC	NC	NC	6.0		
			08:30	200								
			NR		200/90							
			NR		200/90							
			NR		210/90							
			NR		190/100							
			NR		180/90							
			08:15	200	160/85							
			NR		170/90							
			NR		170/90							
			NR		170/90							
			NR		200/195							
			13:00	200	190/90							
			NR		180/90							
			NR		200/100							
			NR		200/95							
			NR		185/95							
			08:25	200	170/85							
			NR		170/85							
			NR		170/85							
			NR		195/100							
			NR		190/100							
			07:00			NC	NC	NC	NC	6.8		
			08:15	200	190/100							
			NR		195/100							
			NR		190/100							
			NR		180/90							
			NR		170/90							
			13:30	200	215/110							
			NR		215/100							
			NR		150/70							
			NR		175/85							
			NR		180/90							
			07:00			NC	NC	NC	NC	7.6		
			08:40	200	200/100							
			NR		160/80							
			NR		170/80							
			NR		160/80							

Sys = systolic, Dia = diastolic, PO4 = phosphate, Na = sodium, K = potassium, Ca = calcium, Hgb = hemoglobin, RxEday = days since final dose of study drug, M = male, F = female, B = Black, C = Caucasian, NC = not collected, NR = not reported, Sit = sitting, Sup = supine, Std = standing

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Table 13. Chronology of Dosing and Selected Data for Case 1 Uncontrolled (continued)

Study Subject	Age/ Sex/ Race	Date	Time	FCM Dose (mg)	B/P Sys/Dia (mmHg)	Blood Chemistry PO4 (mg/dL)	Na (mEq/L)	K (mEq/L)	Ca (mg/dL)	Hgb (g/dL)	Adverse Event Preferred Term	Stop Date (RxEday)
			NR		160/80							
			08:00	100	170/90							
			NR		170/90							
			NR		170/90							
			NR		170/90							
			NR		160/80							
			07:00			NC	NC	NC	NC	10.1		
											Cardiac failure acute	

Sys = systolic, Dia = diastolic, PO4 = phosphate, Na = sodium, K = potassium, Ca = calcium, Hgb = hemoglobin, RxEday = days since final dose of study drug, M = male, F = female, B = Black, C = Caucasian, NC = not collected, NR = not reported, Sit = sitting, Sup = supine, Std = standing

The Investigator was asked to request and provide any additional records, talk to the subject's family physician who completed the death certificate (which indicated that the direct cause of death was heart failure) and to answer the following queries. We were informed by our European development partner that no additional records are available. The Investigator's verbal response to the queries is summarized below.

1. Did she demonstrate progressive signs and symptoms of heart failure prior to the death? *Answer: The patient did not demonstrate any progressive signs and symptoms of heart failure prior to death.*

2. What evidence does the PI and/or family physician have the cause of death was acute heart failure? *Answer: They have no evidence regarding that her death was due to acute heart failure.*

3. Was the clinical progression consistent with progressive deterioration due to heart failure? *Answer: No anticipating signs were seen that could bee (sic) related to acute heart failure.*

4. Was the death anticipated based on her deteriorating course? *Answer: No*

5. What was the probability that the pre terminal event was not heart failure? *Answer: The Investigator could not specify this.*

On (19 days after last dose of FCM), this 54-year-old patient died. The direct cause of death was listed as heart failure by the patient's family physician with preceding causes of atrial fibrillation and initial morbidity of hypertensive disease and end stage chronic renal failure. It is worth noting that this subject had substantial cardiac co-morbidity and important pre-existing risks for a heightened cardiovascular death rate.

Pre-existing cardiac co-morbidity included:

1. Mixed ischemic and uremic cardiomyopathy
2. NYHA Class III CHF
3. Poorly controlled hypertension. Documented blood pressures frequently exceeded a systolic of 200 and diastolic of 100 mmHg.
   Systolic blood pressures greater than 180 mmHg have been demonstrated to increase the relative risk of mortality in hemodialysis patients (Appendix E).13
4. Left ventricular hypertrophy
5. Pericarditis (past history)
6. Atrial fibrillation

Additional pre-existing risk factors for a heightened cardiovascular death rate included:

1. Hemodialysis dependent Chronic Kidney Disease

   Annual overall mortality rates reported from the 2006 US Renal Data System for hemodialysis patients is 18.6% with cardiac events being the leading cause of death.[14] Annual mortality due to cardiovascular causes among white females 45-54 years of age undergoing chronic dialysis is 9%, nearly 90-fold higher than that seen in the age-matched general population.[13] Median survival has been reported to be only 18 months after development of de novo heart failure, far higher than that observed in the general population.[20] This subject's death from acute congestive heart failure, which was unobserved by medical practitioners, was consistent with her pre-study history of ischemic and uremic cardiomyopathy with high-grade NYHA III functional deficits in a patient undergoing chronic hemodialysis.

2. Severe iron deficiency anemia at baseline (hemoglobin of 6.0 mg/dL)

   Mortality estimates in patient populations with chronic kidney disease, especially those with anemia, are considerable, as anemia is a marker of more advanced kidney disease at any level of kidney function. A report by McClellan et al. found that in hospitalized CHF patients with CKD the highest yearly mortality rates (50%; RR 1.6) were found in those with hematocrit <30%.[21]

5.2.2 Independent Expert Review

Independent Clinical Pharmacology Safety Experts Dr. Judith Jones, MD, PhD and Staff, Degge Group

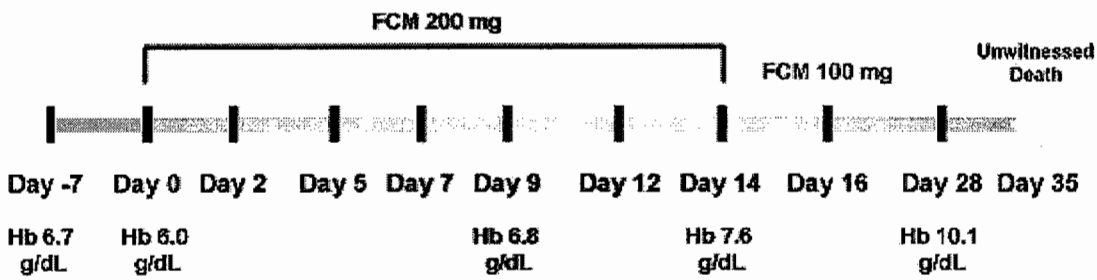
An initial review and an intensive re-review of this case with a focus on cardiovascular features was performed and concluded:

"This 54-year-old female had many serious chronic disorders (renal failure, severe hypertension, cardiac disease) in addition to very severe anemia. Although congestive heart failure presumed, patient found dead at home without further examination, so several factors might have contributed to her death, including(1) MI with arrhythmia, and/or (2) CHF related to her severe hypertension and the anemia, (3) Infection associated with her low WBC. There is no clear basis to relate this event to the FCM."

Summary Representing All Expert Reviews of Case 1 Uncontrolled

Case 1 Uncontrolled is a 54-year-old Romanian female with chronic renal failure undergoing chronic hemodialysis, hypertension, cardiomyopathy (Class III), chronic congestive heart failure, poorly controlled high blood pressure (200 mmHg at study entry) and anemia. She received a series of FCM and her last dose was 100 mg. Over 2 weeks later on [redacted], she *died at home*, an unwitnessed death. Her general practitioner noted initially that she died suffering from acute congestive heart failure. The annual death rate of patients with severe congestive heart failure on chronic hemodialysis is approximately 50%. In the setting of end-stage renal failure with pre-existing heart failure, the cause of death was most likely cardiovascular. Death at home is not unusual. In a third of hemodialysis patients, the cause of death is listed as cardiac, a reflection of the high prevalence of cardiovascular comorbidity in this patient population. The death was judged unrelated to FCM by Investigator, clinical pharmacologist, and nephrologist/iron expert. The death was judged unrelated to known intravenous iron adverse events such as anaphylaxis and hypotension. The death was also deemed unrelated to other study deaths, to non-fatal study adverse events, to low serum phosphate and to preclinical toxicology. A schematic of the subject's timecourse is presented in **Figure 7**.

Figure 7. Schematic of Case 1 Uncontrolled



5.3 Case 2 Uncontrolled

Study Number: VIT-53214
Event: Pulmonary tuberculosis

This 59-year-old female with CKD and anemia was consented on . Her medical history is significant for chronic obstructive bronchitis, coronary heart disease (NYHA II), chronic hepatitis, renal polyneuropathy, glomerulonephritis, and infiltrative tuberculosis of the lung. The patient had multiple extended admissions to the for treatment of symptomatic tuberculosis 3). Her sputum cultures were positive for mycobacterium tuberculosis as recently as . The patient started hemodialysis in

The patient's hemoglobin during her screening visit on was 8.5 g/dL with a TSAT of 6% and serum ferritin of 94 mcg/L. On her hemoglobin was 8.1 g/dL. The patient's iron deficit was calculated to be 1,200 mg.

She received her first dose of FCM on during dialysis and received 5 additional doses of 200 mg FCM during 5 hemodialysis sessions. She received her last dose of FCM on study day 11. Electrocardiograms performed before FCM dosing on and again on were considered abnormal, but not clinically significant

On (study day 9), an abnormal chest x-ray was reported as an adverse event, which was considered by the Investigator to be non-serious, of moderate intensity and unrelated to study drug. No action was taken for this event. She was admitted to the (study day 13) with cough, weakness and dyspnea after exercise and a diagnosis of lung tuberculosis. She was treated with isoniazid, Rifampin, tyrosine, and etambutol. The patient was progressively short of breath and hypoxic during the hospitalization. Her overall clinical course was consistent with deteriorating pulmonary tuberculosis. The last EKG was obtained one day following admission for the tuberculosis exacerbation which was 12 days prior to subject's death and was not significantly different from baseline.

The patient died on (study day 26) due to shortness of breath and progressive respiratory insufficiency secondary to the underlying infiltrating tuberculosis. No autopsy was performed.

The Investigator considers this serious adverse event to be unrelated to study drug.

5.3.1 Sponsor Commentary

Key clinical and laboratory data Case 2 Uncontrolled are summarized in **Table 14**. In short, this was a 59-year-old hemodialysis patient with a pre-treatment history of active tuberculosis, chronic heart disease, obstructive lung disease and infectious hepatitis who died from respiratory failure due to tuberculosis. Despite continued treatment with epoetin beta, administration of FCM prompted little response in hemoglobin, a finding consistent with the subject's burden of infection and co-morbid disease. No relationship between FCM administration and tuberculosis was suspected by the patient's physician. No relationship between tuberculosis and administration of intravenous iron agents of any class has been described in the literature.

Serum phosphate data are not available on this subject. However, it is unlikely a contributing factor, as no hemodialysis subject had a nadir phosphate <2 mg/dL [CTCAE Grade 3] in the VIT-06 safety study. In this study, subject's received a single dose of 15 mg/kg, up to a maximum of 1,000 mg of FCM, comparable to the cumulative 1,200 mg dose received by this patient.

The conclusion of the Investigator that this death was not related to study drug administration is well-supported by the available evidence.

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Table 14. Chronology of Dosing and Selected Data for Case 2 Uncontrolled

Study Subject	Age/ Sex/ Race	Date	Time	FCM Dose (mg)	B/P Sys/Dia (mmHg)	Blood Chemistry PO4 (mg/dL)	Na (mEq/L)	K (mEq/L)	Ca (mg/dL)	Hgb (g/dL)	Adverse Event Preferred Term	Stop Date (RxEday)
VIT-53214												
Case 2 Unc	59/F/C		07:05			NC	NC	NC	NC	8.5		
			07:20			NC	NC	NC	NC	8.1		
			08:20	200								
			NR		130/80							
			NR		130/80							
			NR		130/80							
			NR		150/90							
			NR		150/90							
			07:30			NC	NC	NC	NC	7.6		
			08:20	200								
			NR		140/80							
			NR		155/80							
			NR		150/80							
			NR		150/90							
			NR		150/90							
			08:15	200								
			NR		170/80							
			NR		160/80							
			NR		160/90							
			NR		160/90							
			NR		170/100							
			08:00	200								
			NR		140/80							
			NR		145/80							
			NR		140/80							
			NR		150/80							
			NR		130/80							
			08:00	200								
			NR		140/80							
			NR		150/80							
			NR		140/80							
			NR		130/80							
			NR		140/80							
			NR								X-ray NOS chest abnormal	
			08:25	200								
			NR		140/80							
			NR		140/80							
			NR		150/90							
			NR		130/80							
			NR		145/90							
			11:30								Pulmonary tuberculosis	
			07:10			NC	NC	NC	NC	9.1		

Sys = systolic, Dia = diastolic, PO4 = phosphate, Na = sodium, K = potassium, Ca = calcium, Hgb = hemoglobin, RxEday = days since final dose of study drug, M = male, F = female, B = Black, C = Caucasian, NC = not collected, NR = not reported, Sit = sitting, Sup = supine, Std = standing

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The principal Investigator was asked to summarize his discussions about the clinical course of this subject with the treating physician at the Tuberculosis hospital, to request/provide any additional records and to answer the following queries. The responses are as follows:

1. Was she progressively short of breath and hypoxic during this hospitalization? *Answer: The patient died at another hospital. According to the treating physician and case summary notes from this hospital the patient was progressively short of breath and hypoxic during this hospitalization.*
2. Was the clinical progression during this 2 week period consistent with progressive pulmonary deterioration due to infiltrating pulmonary tuberculosis? *Answer: Yes, the* (sic) *overall her clinical course was consistent with pulmonary tuberculosis progression.*
3. Was the death anticipated based on her deteriorating pulmonary course? *Answer: Yes, the death was anticipated by deteriorating pulmonary tuberculosis*
4. What was the probability that the pre terminal event was somehow cardiac? *Answer: Usually in such cases there is both pulmonary and cardiac insufficiency in advanced stages of disease, so called cardio-pulmonary insufficiency due to cor pulmonale in association with pulmonary hypertension caused by tuberculosis induced fibrosis of perivascular tissue.*

5.3.2 Independent Expert Review

Independent Clinical Pharmacology Safety Experts Dr. Judith Jones, MD, PhD and Staff , Degge Group

An intensive re-review of this case was performed and concluded:

"This very chronically ill and emaciated (BMI 18) 59-year-old female patient with documented tuberculosis in addition to her chronic renal failure requiring dialysis 3x per week since [redacted] was enrolled in the FCM trial and began her 6 treatments of 200 mg FCM with each dialysis in early [redacted] Notable during the injections was her need to use Euphylline for shortness of breath, suggesting some ongoing symptoms of pulmonary difficulty, and indeed she was found to have an abnormal chest film on [redacted] She was hospitalized on [redacted] and found to have severe recurrent pulmonary tuberculosis, and although treatment instituted, she went rapidly downhill and died on [redacted] It is notable that her liver function tests (transaminases) became abnormal during this time, but not her bilirubin. Although her ECGs were noted in the study to be "abnormal but not clinically relevant" the findings did not suggest separate cardiac abnormalities at hospitalization, except prominent P waves consistent with her pulmonary condition. If further Euphylline was used in this very small, emaciated patient, she may have experienced toxicity from this, as well. There was not clear evidence to connect these events with FCM."

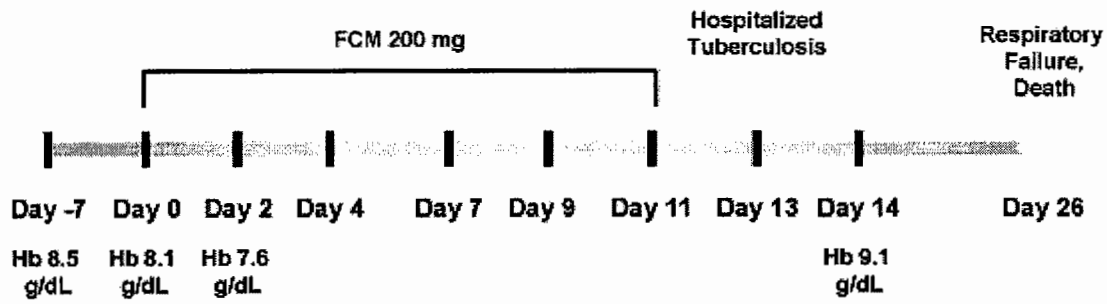
Independent Cardiologist Dr. Leslie Cooper

Dr. Cooper provided official interpretations of the ECGs obtained during the study. The baseline ECG prior to ferric carboxymaltose administration demonstrated changes "consistent with anterolateral myocardial ischemia and/or strain from LVH". Of note, the subject had a documented history of coronary heart disease since [redacted]. The last ECG was obtained one day following admission for the tuberculosis exacerbation which was 12 days prior to subject's death and was also assessed by Dr. Cooper to be "consistent with anterolateral myocardial ischemia and/or strain from LVH". Dr. Cooper did not directly compare the last ECG ([redacted] with the baseline ECG ([redacted]). However, no significant differences between the baseline and last ECG were apparent based on Dr. Cooper's or the sponsor's interpretation.

Summary Representing All Expert Reviews of Case 2 Uncontrolled

Case 2 Uncontrolled is a 59-year-old cachectic female with multiple, extended hospitalizations for active tuberculosis, coronary heart disease, chronic obstructive lung disease, chronic persistent hepatitis, and chronic renal failure undergoing hemodialysis. She received a series of low doses (200mg) FCM. She was hospitalized with active tuberculosis on [redacted] On [redacted], she succumbed to *fatal respiratory failure secondary to tuberculous pneumonia.* The death was judged unrelated to FCM by Investigator, clinical pharmacologist, and nephrologist/iron expert. The death was judged unrelated to known intravenous iron adverse events such as anaphylaxis and hypotension. The Investigator and cardiologist deemed that the death was not due to a primary cardiac event. The death was also deemed unrelated to other study deaths, to non-fatal study adverse events, to low serum phosphate and to preclinical toxicology. A schematic of the subject's study timecourse is presented in **Figure 8**.

Figure 8. Schematic of Case 2 Uncontrolled



5.4 Case 3 Uncontrolled

Study Number: VIT-06
Event: Pneumonia

This 48-year-old female with a six year history of anemia was randomized on [redacted] Her history is significant for gastric bypass for morbid obesity in [redacted] hysterectomy in [redacted], seizure disorder, depression on multiple psychotropic meds, and rapid heartbeat. She received her first blinded infusion of study drug on [redacted] The second blinded infusion of study drug was study day 8 ([redacted]). Per protocol, 1 of the blinded infusions would have been FCM at 15 mg/kg (maximum dose 1,000 mg) and the other blinded infusion would be placebo (normal saline). At the completion of the study, unblinding occurred. This patient received placebo on [redacted] and FCM on [redacted]

She presented to the physician's office on [redacted] (3 days before FCM treatment) with a complaint of a possible bladder infection. Urine multistix showed positive nitrates and leucocytes. She was treated with Levaquin for 5 days and 1 dose of Diflucan for yeast infection. On [redacted] (5 days after FCM) she presented with complaint of right ear pain and was treated with Cortisporin OTIC for 5 days for a right ear infection. She presented again to the same physicians office on [redacted] (25 days after FCM) with a sore throat, cough, and stuffy nose. Her vital signs were T-97.2° F, P- 94, BP 118/70, and oxygen saturation was 97%. Strep test was negative. Urine Multistix showed positive nitrates and trace of leukocytes. She was prescribed Augmentin 875 mg BID for 10 days. On [redacted] (27 days after FCM) her case worker called the ambulance to transport her to the Emergency Department because of shortness of breath, coughing, weakness, and fatigue. O^2 saturation at home was 80% but 40% in the ED. Chest x-ray shows extensive infiltrate involving most of the right lung, consistent with severe right lung pneumonia. She was intubated and a Multi-Med line placed. Soon after placement of the central line she became bradycardic and hypotensive and a code was called. The diagnosis of pneumonia, respiratory failure, and sepsis was made. The patient went into cardiac arrest a second time, all attempts to revive her failed, and she died in the ED. Laboratories were remarkable for a pH of 6.91, PCO_2 of 60, white blood cells of 1.7 with 14 segs and 14 bands, a blood urea nitrogen 42, creatinine 2.4, bicarbonate 12. Cardiac enzymes and BNP (B-Type Natriuretic Peptide) were normal. Electrocardiogram showed a sinus tachycardia. Sputum and two blood cultures were positive for aeromonas hydrophila.

The Investigator considers this serious adverse event (pneumonia) unrelated to study drug.

5.4.1 Sponsor Commentary

Key data for Case 3 Uncontrolled are summarized in **Table 15**. This subject was a 48-year-old, chronically ill woman with a history of recurrent infections who succumbed to Aeromonas hydrophila pneumonia.

Respiratory infection with Aeromonas hydrophila is rare.[22] Infection of both immunocompromised and previously healthy individuals has been reported.[23] Aeromonas hydrophila pneumonia is characterized by rapid onset, necrotizing pneumonitis, fulminant course, and frequently fatal outcome despite use of respiratory support and administration of appropriate antibiotics. No relationship between Aeromonas hydrophila infection, including pneumonia, and either intravenous iron administration or oral iron administration have been described. Moreover, the onset of her infection 27 days after FCM administration precludes any theoretical role that

study drug may conceivably have played as contributing factor. Pharmacokinetic studies (CL-02) confirm that circulating FCM would long before have been absent from the plasma and this subject's TSAT was normal (34%) 13 days prior to hospitalization, effectively excluding super saturation of transferrin as a stimulus to bacterial growth. There is no evidence that FCM or intravenous iron agents of any class increase infection rate.[18,19] Rather, chronic illness, gastric bypass, and repeated prior and current use of broad-spectrum antibiotics may have raised her susceptibility to this unusual organism. The available evidence therefore supports the Investigator's judgment that the infection and resulting death were unrelated to study drug.

Table 15. Chronology of Dosing and Selected Data for Case 3 Uncontrolled

						Blood Chemistry					Adverse Event	
Study Subject	Age/ Sex/ Race	Date	Time	FCM Dose (mg)	B/P Sys/Dia (mmHg)	PO4 (mg/dL)	Na (mEq/L)	K (mEq/L)	Ca (mg/dL)	Hgb (g/dL)	Preferred Term	Stop Date or Time (RxEday)
VIT-06												
Case 3 Unc	48/F/C				112/64 Sit	2.9	141	2.9	8.6	11.4		
					110/74 Sit							
			08:10		114/80 Std							
			08:25	Placebo								
					110/60 Sit							
			08:41		100/60 Std							
					100/64 Sit							
			09:11		100/60 Std							
					98/60 Sit							
			09:41		110/64 Std							
			15:00								Nausea	
			05:00								Cystitis	
											Vaginal	
			05:00								mycosis	
			NR			3.3	139	3.4	8.7	10.8		
					110/60 Sit							
			09:30		114/60 Std							
			09:32	1,000								
					106/60 Sit							
			09:48		104/60 Std							
					100/62 Sit							
			10:18		100/60 Std							
					100/58 Sit							
			10:48		104/62 Std							
			19:00								Ear infection	
					112/74 Sit	2.7	139	3.9	8.6	11.8		
											Upper	
											respiratory	
											tract	
					118/70						infection	
			14:40				142	2.8	7.7	14.1	Pneumonia	

Sys = systolic, Dia = diastolic, PO4 = phosphate, Na = sodium, K = potassium, Ca = calcium, Hgb = hemoglobin, RxEday = days since final dose of study drug, M = male, F = female, B = Black, C = Caucasian, NC = not collected, NR = not reported, Sit = sitting, Sup = supine, Std = standing

A question was posed if the etiology of death might have in fact been an acute inferior wall myocardial infarction or congestive heart failure with the CXR being interpreted mistakenly as pneumonia instead of CHF?

Luitpold responded that this subject presented to the Emergency Department on the day of death with classic pneumonia and septic shock with positive cultures. The following additional detail supports this conclusion:

1. Gram stain was positive for gram negative rods in 2 out of 2 blood smears.
2. Blood culture was positive for *Aeromonas hydrophila* in 2 out of 2 blood cultures.
3. Gram stain of the sputum revealed 4+ white blood cells and 4+ gram negative rods.
4. Sputum culture was also positive for *Aeromonas hydrophila.*
5. CK-MB, troponin and B-type naturetic peptide values were all within normal range.

5.4.2 Independent Expert Review

Independent Cardiologist Leslie T. Cooper, MD

Dr. Cooper reviewed the entire hospital record from the day of death and confirmed that the pre-terminal event was not an acute inferior wall myocardial infarction and/or acute congestive heart failure.

Case Summary:

"Subject was a 48-year-old woman who presented to the [redacted] on [redacted] with severe respiratory distress. The incoming patient report form reported hypoxia, tachycardia, and hypertension (BP 196/142) at 1429. The patient arrived in emergency room 5 at 1440, and underwent initial evaluation at 1443. The initial assessment noted that the patient was pale, cyanotic, and confused with "inappropriate vocalizations" and "thick, copious" sputum. No note was made of chest pain. intravenous access was obtained at 1455, Rocephin was given, and the patient was intubated at approximately 1503. A subclavian central line was placed between 1510 and 1525. The patient has a bradycardic or asystolic, hypotensive cardiac arrest sometime between 1522 and 1535. She received epinephrine, atropine, and high dose dopamine between 1525 and 1543. The code flow sheet noted pulseless electrical activity at 1543. Blood was obtained from the endotracheal tube around 1545. Between 1545 and 1603 she had a tachycardic rhythm and acceptable blood pressure. Despite supplemental oxygen and positive pressure ventilation, she remained hypoxic with an oxygen saturation of 50% to 80%. She arrested again, and at this time a cardiac ultrasound showed no evidence of "cardiac activity" despite epinephrine and atropine. The code was stopped at 1622. Relevant laboratory data include an arterial blood gas (drawn at 1525) with a pH of 6.91 due to combined metabolic and respiratory acidosis (bicarbonate 12, CO2 60). Her PO2 was only 62 despite supplemental oxygen. Her peripheral leukocyte count was decreased at 1.7 with 14% bands, consistent with a severe bacterial infection. Blood cultures grew gram negative rods identified as Aeromonas hydrophila. Sputum gram stain was remarkable for 4+ WBC and 4+ gram negative rods. Sputum culture grew 4+ Aeromonas hydrophila and 4+ E. coli. Chest radiograph revealed an extensive right lung infiltrate, consistent with severe pneumonia. Troponin was less than 0.01 ng/ml and creatinine phosphokinase (CPK)-MB was 1 ng/ml. B-type natruretic peptide was also normal at 94.2 pg/ml. EKG dated [redacted] ay 15:17 revealed sinus tachycardia at 123 bpm with normal intervals, axis, and voltage. There are narrow Q waves in leads II, III, aVF, V5 and V6, with the exception of lead III, these do not exceed 40 ms in width and/or do not exceed 25% of the R wave height. Nonspecific T waves changes are present throughout the inferolateral leads. Compared to the ECG dates [redacted] the Q waves are now less prominent in leads II and III and essentially identical in leads I, V5 and V6.

Discussion:

The question is whether the pre-terminal event was either an inferior wall myocardial infarction or acute congestive heart failure rather than sepsis due to pneumonia. The diagnosis of myocardial infarction requires the triad of a compatible clinical syndrome, such as chest pain or an anginal equivalent, elevated biomarkers of cardiac necrosis, such as troponin or CPK-MB, and new ischemic changes on EKG. None of these three criteria are fulfilled in the present case. The EKG has nonspecific changes in leads III, and aVF which are consistent with severe acidosis. The Q waves were present on the [redacted] EKG and therefore do not reflect acute ischemia. An inferior myocardial infarction could present with bradycardia, however, the patient's initial presentation was with hypertension (at 1429), which is not consistent with severe inferior ischemia or decreased right sided cardiac output. Furthermore, the EKG at 1517, shortly before her cardiac arrest, did not show an inferior or posterior injury pattern. The "thick, copious" sputum was consistent with the radiographic and laboratory data that established the diagnosis of a severe, right lung, gram negative pneumonia. In contrast, respiratory failure from congestive heart failure would have bilateral infiltrates, pleural effusions, and serous, not thick, secretions. Furthermore, congestive heart failure would certainly have been associated with an elevated BNP, which was not the case. In this setting the pulseless electrical activity during the code was likely due to severe acidemia and hypoxia. Therefore, based on these data, the pre-terminal event in this case was a cardiopulmonary arrest in the setting of severe acidosis and hypoxia, which in turn was due to extensive gram negative pneumonia."

Independent Clinical Pharmacologist Safety Experts Dr. Judith Jones, MD, PhD and Staff, Degge Group

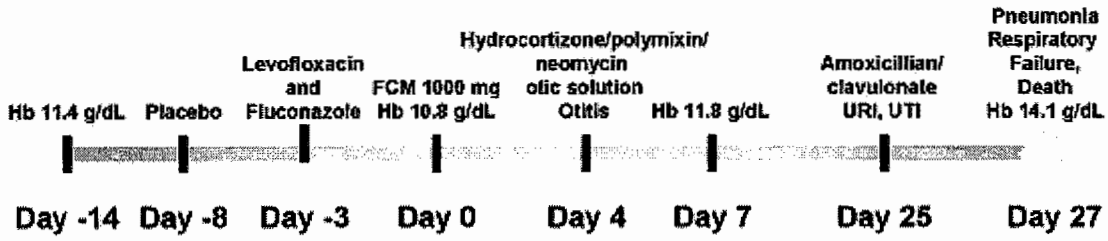
An initial review and an intensive re-review of this case with a focus on cardiovascular features was performed and concluded:

"This 48-year-old female's death was most likely related to severe hypoxemia due to a severe and aggressive aeronmonas (sic) pneumonia infection that likely started before [redacted] It is of note that the patient had a very low WBC at the time of ER admission and that prior WBC's were also low, possibly contributing to recurrent infections and the occurrence of this unusual pathogen. Her recent use of levaquin, which can be associated with agranulocytosis could be hypothesized as a possibly contributor to the leucopenia and subsequent infection. It is also possible that her beta blocker, sotolol, might have contributed either to exacerbate her pulmonary function difficulty, if it was being taken, or if not, contributed to her tachycardia due to discontinuation symptoms. There was no evidence of actual cardiac damage (normal enzymes). Further, there was no evidence to link these events to the FCM injection."

Summary Representing All Expert Reviews of Case 3 Uncontrolled

Case 3 Uncontrolled is a 48-year-old female with recurrent infections, depression, seizures, gastric bypass for morbid obesity. She suffered from a series of infections (cystitis, vaginitis, otitis, URI, UTI). She received a single administration of FCM 1000mg. About 1 month later, she succumbed to death from respiratory failure from *bacteremic Aeromonas pneumonia with neutropenia and septic shock* (anion gap acidosis, hypoxia, respiratory failure, and hypotension). The death was judged unrelated to FCM by Investigator, clinical pharmacologist, and nephrologist/iron expert. The death was judged unrelated to known intravenous iron adverse events such as anaphylaxis and hypotension. The cardiologist deemed that the death was not due to a primary cardiac event. The death was also deemed unrelated to other study deaths, to non-fatal study adverse events, to low serum phosphate and to preclinical toxicology. A schematic of the subject's study timecourse is presented in **Figure 9**.

Figure 9. Schematic of Case 3 Uncontrolled



5.5 Case 4 Uncontrolled

Study Number: VIT-05
Event: Perforated Colon

This 86-year-old male was randomized to study VIT-04 on and continued on the VIT-05 extension study.

His past medical history is significant for ND-CKD ( ), diabetes mellitus type II, nephrolithiasis ( ), anemia, CAD, MI, hypertension, hyperlipedmia, GERD, appendectomy, hypothyroidism, hepatic abscess, diverticulosis of sigmoid colon, rheumatoid arthritis, gout, and insomnia.

He was randomized originally to the comparator arm with ferrous sulfate 325mg p.o. t.i.d. x 6 weeks during the VIT-04 study. He continued on the VIT-05 extension study and received a total dose of 1,500mg of FCM. He received his first dose of FCM (1000 mg intravenous) on (study day 0). On (study day 86), he received 500 mg FCM in 100 ml normal saline given intravenously over 15 minutes.

He was admitted to the hospital on study (study day 181) by EMS for not feeling well and being "unresponsive" with a week of decreased appetite. Upon arrival to the ED his temperature was 97.6, pulse 102, BP 86/42, respiratory rate of 20, and pulse oximetry of 96% on 2 L. EKG revealed atrial fibrillation with RBBB, rate 141 beats per minute with no ST-T wave abnormality. Chest x-ray showed free intraperitoneal air, suggesting bowel perforation. A prior abdominal CT scan without contrast done on to evaluate flank pain and history of kidney stones also showed diffuse diverticulosis involving the sigmoid colon without surrounding inflammatory changes. A prior hospital admission in for abdominal pain and leukocytosis resulted in a diagnosis of hepatic abscess. During this hospitalization, he was admitted to the ICU, received several units of blood, and had an exploratory laparotomy and sigmoid resection with colostomy on (study day 182). The operative findings were abdominal abscess with multiple areas of loculation and small bowel and a large perforation was identified in the sigmoid colon, which was actively leaking stool. There were extensive amounts of inflammatory changes on the small bowel and distal ileum with no additional perforations or abnormalities. He died on postoperative day 2; (study day 182 and ninety eight days after his last dose of FCM). Final surgical pathology report of the sigmoid colon specimen reveals "diverticulosis with multiple foci of acute diverticulitis and two separate ruptured diverticular perforations." There is no neoplasm and no findings to suggest chronic idiopathic inflammatory bowel disease.

The patient was discontinued from the study at the time of intervention with blood transfusions.

The Investigator considers this serious adverse event (perforated colon) unrelated to study drug. This study subject's prior history of hospitalization for abdominal pain resulting in a diagnosis of hepatic abscess in ; subsequently, with an abdominal CT (in) showing diffuse diverticulosis involving the sigmoid colon was confirmed with the Investigator by phone on .

Death certificate received on revealed that the certifying physician deemed the death is due primarily to bowel obstruction (onset days) in the setting of pre-existing renal insufficiency, coronary artery disease, and cardiomyopathy.

5.5.1 Sponsor Commentary

Key data for Case 4 Uncontrolled are summarized in **Table 16**. In short, this subject was an 86-year-old man with a history of diverticulosis, diverticulitis, chronic kidney disease, chronic heart disease and previous evidence of abdominal infection who died after suffering a large perforation of the colon secondary to diverticulosis and diverticulitis, complicated by peritonitis, intra-abdominal absences, and sepsis. His multiple medications before study entry included daily prednisone. The diagnosis was established conclusively by direct inspection and colectomy during exploratory laparatomy.

No other causal factors are apparent or are needed to explain the patient's presentation. Although the patient received both oral iron and, afterwards, FCM, neither the timing nor findings of the presentation are consistent with known or theoretical effects of study drug, other intravenous iron agents, or oral iron agents. Moreover, the 98-day period between the last dose of FCM and the onset of the patient's complaints effectively excludes any etiologic relationship to either FCM or oral ferrous sulfate. The judgment of the Investigator that the event was unrelated to study drug is fully supported by the evidence.

Table 16. Chronology of Dosing and Selected Data for Case 4 Uncontrolled

Study Subject	Age/ Sex/ Race	Date	Time	FCM Dose (mg)	B/P Sys/Dia (mmHg)	Blood Chemistry PO4 (mg/dL)	Na (mEq/L)	K (mEq/L)	Ca (mg/dL)	Hgb (g/dL)	Adverse Event Preferred Term	Stop Date or Time (RxEday)
VIT-05												
Case 4 Unc	86/M/C		15:45			3.4	140	4.1	8.8	9.8		
					92/48 Sit							
			14:50		92/56 Std							
			14:55	1,000								
					96/58 Sit							
			15:15		102/60 Std							
					102/58 Sit							
			15:45		102/64 Std							
					102/68 Sit							
			16:15		98/62 Std							
			14:40		106/60	2.0	142	3.6	8.3	11.1		
			7:28		112/64	2.3	141	3.4	8.9	11.5		
			15:25		164/52	3.1	144	3.7	8.6	10.4		
					112/64 Sit							
			14:25		108/60 Std							
			14:30	500								
					112/60 Sit							
			14:50		106/54 Std							
					102/54 Sit							
			15:20		98/56 Std							
					98/56 Sit							
			15:50		102/60 Std							
			15:50			2.5	138	4.3	8.6	11.7		
			16:45			3.4	141	3.8	9.2	11.3		
			NR								Fall	
			NR								Pain	
			15:40			3.0	140	3.8	8.8	9.5		
			NR								Excoriation	
			15:45			3.2	142	3.5	4.9	9.2		
			NR			4.0	133	3.6	6.4	12.2	Skin ulcer	
			13:32		86/42	NC	139	3.6	NC	9.4	Sigmoid Perforation	
			00:05			NC	148	3.2	NC	8.9		
			04:32			4.5	148	4.0	NC	12.7		

Sys = systolic, Dia = diastolic, PO4 = phosphate, Na = sodium, K = potassium, Ca = calcium, Hgb = hemoglobin, RxEday = days since final dose of study drug, M = male, F = female, B = Black, C = Caucasian, NC = not collected, NR = not reported, Sit = sitting, Sup = supine, Std = standing

5.5.2 Independent Expert Review

Independent Clinical Pharmacology Safety Expert Dr. Judith Jones, MD, PhD and Staff, Degge Group

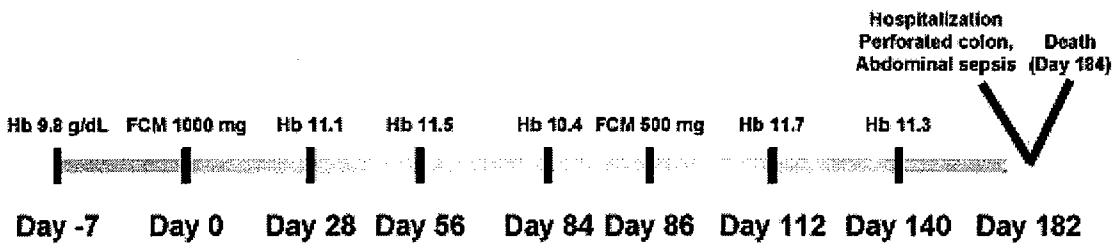
An initial review and an intensive re-review of this case with a focus on cardiovascular features was performed and concluded:

"This 86-year-old gentleman succumbed over 3 months after his last FCM treatment. He had a history of ND-CKD since [redacted], as well as severe rheumatoid arthritis, hypertension and many other chronic disorders. After losing his appetite and not feeling well, he was hospitalized and found to have abdominal masses and underwent laparotomy, where a perforated sigmoid colon and abdominal abscess were found, and despite treatment, he died shortly thereafter (hospital details of course of treatment not available). Although his ECG showed a right bundle branch block, and at hospitalization he had rapid atrial fibrillation with some ST changes, there is little suggestion based upon available records, that a cardiac disorder per se, contributed to his demise. It is notable that the patient was on a very large number of medications, including daily prednisone, which may have contributed to his risk for his abdominal infection. There is no evidence to relate this death to the patient's FCM injections from this review."

Summary Representing All Expert Reviews of Case 4 Uncontrolled

Case 4 Uncontrolled is an 86-year-old male with chronic kidney disease, diverticulosis, diverticulitis, coronary artery disease, and previous hepatic abscess. The history of previous hepatic abscess suggested that the patient had previous diverticulitis which may have penetrated, infected and led to downstream abscess formation. On [redacted] he was hospitalized for a perforated colon and abdominal sepsis. The death was judged unrelated to FCM by Investigator, clinical pharmacologist, and nephrologist/iron expert. The death was judged unrelated to known intravenous iron adverse events such as anaphylaxis and hypotension. The death was also deemed unrelated to other study deaths, to non-fatal study adverse events, to low serum phosphate and to preclinical toxicology. A schematic of the subject's study timecourse is presented in **Figure 10**.

Figure 10. Schematic of Case 4 Uncontrolled



5.6 Case 5 Uncontrolled

Study Number: VIT-05
Events: Upper GI bleeding, stress gastritis, anoxic encephalopathy

This 64-year-old female was randomized to the VIT-04 study on the FCM arm on and continued on the VIT-05 extension study. Her past medical history is significant for ND-CKD, diabetes mellitus type II with nephritis, anemia, hypertension, hyperlipedmia, chronic lower extremity edema, and frequent bladder infections.

Baseline hemoglobin's were 11.3 and 10.7 g/dL, TSAT 18% and ferritin 182 ng/mL. She was randomized originally to the FCM arm and received 1,000 mg intravenous during the VIT-04 study. She continued on the extension study and received a total dose of 1,500 mg of FCM. On study day 143, forty-six (46) days prior to her death on study day 189, she received her last 500 mg of FCM. The total FCM dose she received for both studies is 2,500 mg.

She was admitted to the hospital on (study day 171) for surgical evaluation for adenopathy noted in her chest and mesentery on CT scan. On study day 172, she underwent elective laparotomy and biopsy of mesenteric lymph node. Pathology report of the mesenteric lymph nodes reveals granulomatous lymphadenitis. Aside from reported lymphedema, her postoperative course is acute and is remarkable for a declining overall clinical state with altered mental status. At the time, it was felt that she was probably overmedicated with pain medication. Her morphine sulfate dose was cut and fluids were started. She had received only 2 doses of Toradol prior to it being discontinued. Labs were hemoglobin 9.7, BUN 40, Creatinine 3.1. Chest X-ray shows bilateral hilar fullness, some evidence of congestive heart failure and cephalization of flow. Her carotids revealed bilateral stenosis in the 60-70% range. Doppler was negative for DVT. She was found to be in respiratory acidosis. Post-operative Day 2, her confusion improved clinically but she continued to be in a condition where she is not able to give a history. Labs were hemoglobin 10.2, BUN 42, Creatinine 3.2, and CPK 579. Blood culture was negative. She was afebrile. She received 1 unit of PRBCs. On Post-operative Day 4, GI was consulted for heme positive melenic type stools but GI work-up with endoscopy was deferred due to recent surgery. On Post-operative day 5, ACLS was performed and she was intubated for cardiac arrest in the setting of significant high volume bloody bowel movements, sudden loss of consciousness, and drop in blood pressure. She remained on ventilator support due to acute respiratory failure and cardiac arrest. Her post-transfusion labs were hemoglobin 11.1, Troponin 0.03, BUN 21, Creatinine 1.6, and WBC 20.3. Her hemoglobin was 5.5 after GI bleed. She was then transfused with 9 more units of PRBCs and was found to have massive GI bleed secondary to stress gastritis under endoscopy. On Post-operative Day 9, she remained unresponsive status post arrest and was diagnosed with hypoxic encephalopathy. Her post-transfusion labs were hemoglobin 11.2, BUN 12, Creatinine 1.3. Head CT did not reveal a brain stem infarct. On Post-operative Day 17, her family elected to withdraw life support due to her persistent vegetative state. She was transferred out of the ICU and died. The probable cause of death was anoxic encephalopathy.

The patient was discontinued from the study at the time of intervention with blood transfusions.

The Investigator considers these serious adverse events upper GI bleeding, stress gastritis, and anoxic encephalopathy status-post lymph node biopsy unrelated to study drug.

5.6.1 Sponsor Commentary

Key data for Case 5 Uncontrolled is summarized in **Table 17**. In short, this was a 64-year-old woman with anemia associated with chronic kidney disease, not requiring dialysis who received her last dose of FCM 46 days prior to her death. After exploratory laparotomy for unexplained adenopathy, she suffered an acute arrest in association with massive upper GI bleeding, developed hypoxic encephalopathy after the arrest, a persistent vegetative state was diagnosed, and she died after discontinuation of life support. The cause of the arrest is known to be GI bleeding, the cause of GI bleeding was identified by direct endoscopic imaging as gastritis. Though she received FCM in both the primary and extension studies for CKD-associated anemia, there is no conceivable causal relationship between study drug administration and the anatomic GI lesion, gastritis. Furthermore, there is no literature to provide a theoretical causal link between administration of any intravenous iron agent and gastritis, gastrointestinal bleeding of other etiologies, or the patient's pathologic diagnosis on laparoscopy, granulomatous lymphadenitis. These findings are consistent with the Investigator's judgment that death was unrelated to study drug administration.

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Table 17. Chronology of Dosing and Selected Data for Case 5 Uncontrolled

Study Subject	Age/ Sex/ Race	Date	Time	FCM Dose (mg)	B/P Sys/Dia (mmHg)	Blood Chemistry PO4 (mg/dL)	Na (mEq/L)	K (mEq/L)	Ca (mg/dL)	Hgb (g/dL)	Adverse Event Preferred Term	Stop Date or Time (RxEday)
VIT-05/ Case 5 Unc	64/F/ C		08:30							11.3		
			08:45			4.2	135	4.6	9.2	10.7		
			14:10		137/75 Sit 128/71 Std							
			14:22	1,000								
			14:37		116/64 Sit 128/73 Std							
			15:07		123/66 Sit 131/72 Std							
			15:37		128/67 Sit 124/62 Std							
			NR								Abdominal pain upper	
			08:45		132/52 Sit	4.5	135	4.3	9.7	11.6		
			NR								Bursitis	
			NR								Urinary tract infection	
			NR								Headache	
			08:30		117/66 Sit 109/67 Std	4.8	136	4.6	9.6	11.9		
			NR								Asthenia	
			NR								Dizziness	
			08:18				140	4.7	9.6	12.0		
			08:30		126/68 Sit 120/61 Std					12.0		
			NR								Urinary tract infection	
			08:40		131/67 Sit	3.2	136	4.3	8.9	11.4		
			08:08		145/75 Sit 129/69 Std							
			08:14	500								
			08:29		117/66 Sit 116/66 Std							
			08:59		120/68 Sit 113/62 Std							
			09:29		124/64 Sit 119/66 Std							
											Arthralgia	
			08:30		111/55 Sit	4.6	137	4.1	9.0	11.8		
			07:57		114/50 Sit 120/42 Std							
			08:24	500								
			08:39		103/53 Sit 125/60 Std							
			09:09		111/58 Sit 119/63 Std							
			09:39		100/53 Sit 103/62 Std							

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Table 17. Chronology of Dosing and Selected Data for Case 5 Uncontrolled (Continued)

Study Subject	Age/ Sex/ Race	Date	Time	FCM Dose (mg)	B/P Sys/Dia (mmHg)	Blood Chemistry PO4 (mg/dL)	Na (mEq/L)	K (mEq/L)	Ca (mg/dL)	Hgb (g/dL)	Adverse Event Preferred Term	Stop Date (RxEday)
VIT-05												
Case 5 Unc			08:30		144/66 Sit	3.6	136	3.9	9.1	11.5		
			08:40		119/61 Sit	4.8	138	3.9	9.6	10.5		
			09:41							10.2		
			08:30		110/54 Sit	4.1	138	4.2	9.8	10.6		
			NR								Bladder disorder	
			NR							10.4		
.	64/F/C		09:43							10.3		
			09:05		92/51 Sit	4.5	139	4.0	10.5	11.6		
											Hypotension	
			NR									
					121/53 Sit							
			09:40		88/51 Std							
			09:55	500								
					94/52 Sit							
			10:10		103/47 Std							
					99/53 Sit							
			10:40		101/52 Std							
					96/54 Sit							
			11:10		100/56 Std							
			10:20							10.9		
			NR				132	4.6		9.7	Lymphoedema	
			NR							10.2	Upper gastrointestinal hemorrhage	
											Gastritis	
			NR							5.5		
			NR							11.2		
											Anoxic encephalopathy	

Sys=systolic, Dia=diastolic, PO4=phosphate, Na=sodium, K=potassium, Ca=calcium, Hgb=hemoglobin,
RxEday = days since final dose of study drug, M=male, F=female, B=Black, C=Caucasian, NC=not collected, NR=not reported,
Sit=sitting, Sup=supine, Std=standing

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5.6.2 Independent Expert Review

Independent Clinical Pharmacologist Safety Experts Dr. Judith Jones, MD, PhD and Staff, Degge Group

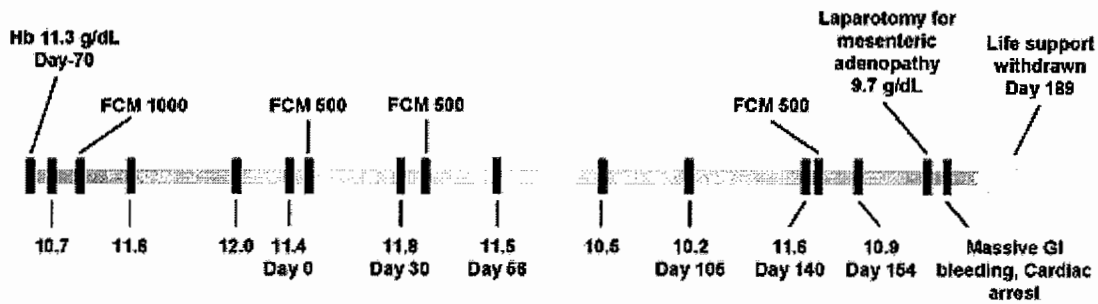
An initial review and an intensive re-review of this case with a focus on cardiovascular features was performed and concluded:

"This obese 64-year-old female with diabetes and Stage II renal disease, hypertension, hyperlipidemia and recurrent bladder infections was in an FCM trial and received a total dose of 2500 mg of FCM. Approximately 1 month after her last dose, she underwent elective surgery for biopsy of an abdominal lymph node found at the time of her cholelithiasis diagnosis in [redacted] The node was excised and showed granulomatous process. Postoperatively, the patient deteriorated. There is no clear explanation for this, but discontinuation of her many drugs may have contributed to this, e.g., amitryptiline, but this is only remotely likely."

Summary Representing All Expert Reviews of Case 5 Uncontrolled

Case 5 Uncontrolled is a 64-year-old female with CKD Stage 2, diabetes, hypertension, hyperlipidemia, chronic edema, recurrent urinary tract infections. Over a period of 8 months, there was a rise and fall of hemoglobin levels, suggesting recurrent GI bleeding. IDA in postmenopausal women, as in men, arises primarily from a GI source. In [redacted] the patient underwent laparotomy for mesenteric adenopathy. Post-operatively, she had melena and then was found to have *massive GI bleeding resulting in cardiac arrest.* On [redacted] life support was withdrawn and the patient expired. The death was judged unrelated to FCM by Investigator, clinical pharmacologist, and nephrologist/iron expert. The death was judged unrelated to known intravenous iron adverse events such as anaphylaxis and hypotension. The death was also deemed unrelated to other study deaths, to non-fatal study adverse events, to low serum phosphate and to preclinical toxicology. A schematic of the subject's study timecouse is presented in **Figure 11**.

Figure 11. Schematic of Case 5 Uncontrolled



6.0 SUMMARY AND CONCLUSIONS (REPEATED)

There was 1 death out of 1052 FCM treated subjects in the postpartum/HUB population, 773 of which were in controlled studies. In all controlled clinical trials, including high and low risk populations, 5 deaths occurred in the FCM treated group and 1 in the comparator group. Three of the deaths (3/1230) in the FCM arm were likely of cardiac etiology (by different mechanisms dilated postpartum cardiomyopathy, myocardial infarction and cardiac arrest) vs. one (1/1002) in the control arm (congestive heart failure). Five deaths occurred in uncontrolled trials. Considering all controlled and uncontrolled studies combined, there were over twice as many subjects, with over twice the length of observation, with over twice as many high risk chronic kidney disease (CKD) patients treated with FCM compared to the control groups. The CKD population has a baseline annual mortality risk of 18.6% for hemodialysis and 7.5% for non-dialysis dependent CKD patients. These mortality risks are much higher than for post-partum/HUB patients.

The potential predictive value of anaphylaxis, bioactive iron reactions, rate of hemoglobin rise, hemoglobin >13 g/dL, hypophosphatemia, baseline mortality risk and FCM dose on the mortality rate was explored. No death was consistent with the expected timing of anaphylaxis or bioactive iron reactions in relation to drug administration. No death was consistent with an allergic, anaphylactic, or bioactive iron reaction mechanism. Serious adverse event rates were associated with lower rather than higher observed hemoglobin levels, presumably reflecting the increased disease burden associated with serious anemia. The deaths occurred in subjects for whom the observed phosphate values at the time of the serious adverse event leading to death were not significantly low, or in subjects whose death occurred too early after FCM administration for hypophosphatemia to have developed. The overall observed mortality rate did not appear related to number of doses, total dose, maximum single dose and size of last administered dose. The observed interval between study drug administration and death is not compatible with the known toxicity of IV iron agents, the interval varied from 1 to 98 days and the pattern is not compatible with the known pharmacokinetic and pharmacodynamic characteristics of FCM.

A clear mechanism for the cause of death, unrelated to iron therapy, was established in 8 out of the 10 FCM treated cases. The remaining 2 deaths occurred in subjects with established pre-existing cardiac and other significant co-morbidities which are more than sufficient to explain these 2 deaths. These mechanisms of death share no pattern.

The mortality rate was related primarily to the baseline mortality risk of the clinical trial populations. That is, the mortality rate was highest in the HD and ND-CKD populations and lowest in the postpartum and HUB populations.

The observed incidence rates in the randomized controlled trials for all cause mortality, all cause mortality within 30 days after the last dose of study drug, and cardiac mortality are small and within statistical expectation (Fishers exact p=0.2328, 0.3874 and 0.6325, respectively). There was a 42% probability of not observing a death in the control group in the postpartum/HUB population.

The heterogeneity of intrinsic mortality risk across populations and the low observed incidence rates of death within populations minimize the value of statistical comparisons and indicate the need for a thorough clinical review of each death to assess potential causality. The multiple external, independent experts drew the following conclusions about the individual deaths:

- No death was consistent with any known adverse effect of FCM or any intravenous iron agent at any dose or any rate of administration

- No death was consistent with any known pharmacokinetic and pharmacodynamic characteristics of FCM or any class of iron agent
- No deaths shared significant features with other deaths except for the frequent finding of a high comorbid disease burden that is characteristic of the study population
- No death lacked explanation

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