CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-135 / S-008

Trade Name: **Venofer**

Generic Name: **Iron Sucrose Injection, USP**

Sponsor: **Luitpold Pharmaceuticals, Inc.**

Approval Date: **June 17, 2005**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-135 / S-008

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-135 / S-008

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-135/S-008

Luitpold Pharmaceuticals, Inc.
Attention: Marsha E. Simon, CQA
1000 Madison Avenue
Norristown, PA 19403

Dear Ms. Simon:

Please refer to your supplemental new drug application dated August 15, 2003, received August 18, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Venofer® (Iron Sucrose Injection, USP).

We acknowledge receipt of your submissions dated December 16, 2004, January 24, March 24, April 11, May 23, June 14, June 16, and June 17, 2005

Your submission of December 16, 2004 constituted a complete response to our June 18, 2004 action letter.

This supplemental new drug application provides for the use of Venofer® (Iron Sucrose Injection, USP) for the treatment of iron deficiency anemia in the following patients:

- non-dialysis dependent chronic kidney disease (NDD-CKD) patients receiving an erythropoietin
- non-dialysis dependent chronic kidney disease (NDD-CKD) patients not receiving an erythropoietin.

Recommended dosing in these patients is a total cumulative dose of 1000 mg over a 14 day period as a slow IV injection undiluted over 2 to 5 minutes on 5 different occasions within a 14 day period.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the submitted labeling (package insert submitted June 17, 2005).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 21-135/S-008.**" Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages birth to < 2 years and deferring pediatric studies for ages ≥ 2 years to < 16 years for this application.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The statuses of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

1. Deferred pediatric study under PREA for a pharmacokinetic study of Venofer administration to adolescent non-dialysis dependent chronic kidney disease (NDD-CKD) patients, ≥ 12 years to < 16 years of age, receiving or not receiving erythropoietin.

Final Report Submission: December 31, 2010

2. Deferred pediatric study under PREA for the treatment of iron deficiency anemia in non-dialysis dependent chronic kidney disease (NDD-CKD) pediatric patients ages ≥ 2 years to < 12 years receiving or not receiving erythropoietin.

Final Report Submission: December 31, 2010

Submit final study reports to this NDA. For administrative purposes, all submissions related to these pediatric postmarketing study commitments must be clearly designated "**Required Pediatric Study Commitments**".

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Alice Kacuba, Regulatory Health Project Manager, at (301) 827-9334.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kathy Robie-Suh
6/17/05 06:54:56 PM
signing for Dr. Joyce Korvick

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-135 / S-008

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-135/S-008

Luitpold Pharmaceuticals, Inc.
c/o Sonneschein, Nath & Rossenthal
Attention: Peter S. Reichertz, Esq.
1301 K Street, N.W.
Suite 600, East Tower
Washington, DC 2005

Dear Mr. Reichertz:

Please refer to your supplemental new drug application dated August 15, 2003, received August 18, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Venofer® (Iron Sucrose Injection, USP).

We acknowledge receipt of your submissions dated February 20, 2004, February 26, 2004, and May 27, 2004.

This supplemental new drug application proposes the use of Venofer® (Iron Sucrose Injection, USP) for the 200 mg dose in the management of anemia in patients receiving erythropoietin for chronic kidney disease not undergoing hemodialysis.

We completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

1. Only one study was conducted in patients with chronic kidney disease not on dialysis. The study failed to demonstrate that Venofer is superior to oral iron in increasing hemoglobin at Day 43 from baseline as planned in the study protocol. The primary efficacy results showed that the difference in mean change in hemoglobin from baseline between Venofer and oral iron groups was not statistically significant (1.0 g/dL vs. 0.7g/dL, p=0.14).

2. Initiation of epoetin therapy in the majority of study patients (83% in the Venofer group and 90% in the oral iron group) during the study may have contributed significantly to an increase in hemoglobin at Day 43 from baseline in both treatment groups. Any effect of iron treatment in either group is confounded by the concomitant initiation of epoetin.

3. A significant proportion of randomized patients were not included in the primary efficacy analysis in the study [26% (14/53) in the Venofer group and 12% (6/49) in the oral iron group)].

4. In the study, patients in the Venofer treatment group experienced more adverse events (except for gastrointestinal disorders), serious adverse events, and premature discontinuation due to adverse events than did patients in the oral treatment group.

5. Safety information in chronic kidney disease patients not on dialysis is limited.

To resolve the clinical deficiencies, you should conduct an adequate and well-controlled study to support the efficacy and safety of Venofer for the treatment of iron deficiency in chronic kidney disease patients not on dialysis. The study should be a randomized, parallel group, controlled study. The study subjects should be iron deficient patients with chronic kidney disease who are not on dialysis, who have received epoetin therapy with a stable dose for at least 3 months before the study, and who will maintain the previous epoetin dose as much as possible during the study.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Tanya Clayton, B.S., Regulatory Project Manager, at (301) 827-4005.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Justice
6/18/04 10:44:55 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-135 / S-008

LABELING

Venofer®

DESCRIPTION

Venofer® (iron sucrose injection, USP) is a brown, sterile, aqueous, complex of polynuclear iron (III)-hydroxide in sucrose for intravenous use. Iron sucrose injection has a molecular weight of approximately 34,000 – 60,000 daltons and a proposed structural formula:

$[Na_2Fe_5O_8(OH) \cdot 3(H_2O)]_n \cdot m(C_{12}H_{22}O_{11})$

where: n is the degree of iron polymerization and m is the number of sucrose molecules associated with the iron (III)-hydroxide.

Each mL contains 20 mg elemental iron as iron sucrose in water for injection. Venofer® is available in 5 mL single dose vials (100 mg elemental iron per 5 mL). The drug product contains approximately 30% sucrose w/v (300 mg/mL) and has a pH of 10.5-11.1. The product contains no preservatives. The osmolarity of the injection is 1250 mOsmol/L.

Therapeutic class: Hematinic

CLINICAL PHARMACOLOGY

Pharmacodynamics: Following intravenous administration of Venofer®, iron sucrose is dissociated by the reticuloendothelial system into iron and sucrose. In 22 hemodialysis patients on erythropoietin (recombinant human erythropoietin) therapy treated with iron sucrose containing 100 mg of iron, three times weekly for three weeks, significant increases in serum iron and serum ferritin and significant decreases in total iron binding capacity occurred four weeks from the initiation of iron sucrose treatment.

Pharmacokinetics: In healthy adults treated with intravenous doses of Venofer®, its iron component exhibits first order kinetics with an elimination half-life of 6 h, total clearance of 1.2 L/h, non-steady state apparent volume of distribution of 10.0 L and steady state apparent volume of distribution of 7.9 L. Since iron disappearance from serum depends on the need for iron in the iron stores and iron utilizing tissues of the body, serum clearance of iron is expected to be more rapid in iron deficient patients treated with Venofer® as compared to healthy individuals. The effects of age and gender on the pharmacokinetics of Venofer® have not been studied.

Venofer® is not dialyzable through CA210 (Baxter) High Efficiency or Fresenius F80A High Flux dialysis membranes. In in vitro studies, the amount of iron sucrose in the dialysate fluid was below the levels of detection of the assay (less than 2 parts per million).

Distribution: In healthy adults receiving intravenous doses of Venofer®, its iron component appears to distribute mainly in blood and to some extent in extravascular fluid. A study evaluating Venofer® containing 100 mg of iron labeled with $^{52}Fe/^{59}Fe$ in patients with iron deficiency shows that a significant amount of the administered iron distributes in the liver, spleen and bone marrow and that the bone marrow is an iron trapping compartment and not a reversible volume of distribution.

Metabolism and Elimination: Following intravenous administration of Venofer®, iron sucrose is dissociated into iron and sucrose by the reticuloendothelial system. The sucrose component is eliminated mainly by urinary excretion. In a study evaluating a single intravenous dose of Venofer® containing 1,510 mg of sucrose and 100 mg of iron in 12 healthy adults (9 female, 3 male: age range 32-52), 68.3% of the sucrose was eliminated in urine in 4 h and 75.4% in 24 h. Some iron also is eliminated in the urine. Neither transferrin nor transferrin receptor levels changed immediately after the dose administration [1]. In this study and another study evaluating a single intravenous dose of iron sucrose containing 500-700 mg of iron in 26 anemic patients on erythropoietin therapy (23 female, 3 male; age range 16-60), approximately 5% of the iron was eliminated in urine in 24 h at each dose level [2].

Drug-drug Interactions: Drug-drug interactions involving Venofer® have not been studied. However, like other parenteral iron preparations, Venofer® may be expected to reduce the absorption of concomitantly administered oral iron preparations.

CLINICAL TRIALS

Venofer® is used to replenish body iron stores in non-dialysis dependent chronic kidney disease (NDD-CKD) patients receiving erythropoietin and in NDD-CKD patients not receiving erythropoietin, and in hemodialysis dependent chronic kidney disease (HDD-CKD) patients receiving erythropoietin. Iron deficiency may be caused by blood loss during dialysis, increased erythropoiesis secondary to erythropoietin use, and insufficient absorption of iron from the gastrointestinal tract. Iron is essential to the synthesis of hemoglobin to maintain oxygen transport and to the function and formation of other physiologically important heme and non-heme compounds. Most dialysis patients require intravenous iron to maintain sufficient iron stores.

Five clinical trials were conducted to assess the safety and efficacy of Venofer®. Four studies were conducted in the United States (390 patients) and one was conducted in South Africa (131 patients).

Study A: Hemodialysis Dependent Chronic Kidney Disease (HDD–CKD)

Study A was a multicenter, open-label, historically-controlled study in 101 hemodialysis patients (77 patients with Venofer® treatment and 24 in the historical control group) with iron deficiency anemia. Eligibility for Venofer® treatment included patients undergoing chronic hemodialysis three times weekly, receiving erythropoietin, hemoglobin concentration greater than 8.0 and less than 11.0 g/dL for at least two consecutive weeks, transferrin saturation < 20%, and serum ferritin < 300 ng/mL. The mean age of the patients in the treatment group was 65 years with the age range being 31 to 85 years of age. The erythropoietin dose was to be held constant throughout the study. The protocol did not require administration of a test dose; however, some patients received a test dose at the physician's discretion. Exclusion criteria included significant underlying disease, asthma, active inflammatory disease, or serious bacterial or viral infection. Venofer® 5 mL (one vial) containing 100 mg of elemental iron was administered through the dialysis line at each dialysis session either as slow injection or a saline diluted slow infusion for a total of 10 dialysis sessions with a cumulative dose of 1000 mg elemental iron. A maximum of 3 vials of Venofer® was administered per week.

No additional iron preparations were allowed until after the Day 57 evaluation. The mean change in hemoglobin from baseline to Day 24 (end of treatment), Day 36, and Day 57 was assessed. The historical control population consisted of 24 patients with similar ferritin level as patients treated with Venofer®, who were off intravenous iron for at least 2 weeks and who had received erythropoietin therapy with hematocrit averaging 31-36 for at least two months prior to study entry. The mean age of

patients in the historical control group was 56 years, with an age range of 29 to 80 years. Patient age and serum ferritin level were similar between treatment and historical control patients. Of the 77 patients in the treatment group, 44 (57%) were male and 33 (43%) were female. The mean baseline hemoglobin, hematocrit, were higher and erythropoietin dose was lower in the historical control population than the Venofer® treated population.

Patients in the Venofer® treated population showed a statistically significantly greater increase in hemoglobin and hematocrit than did patients in the historical control population. See Table 1.

Table 1: Changes from Baseline in Hemoglobin and Hematocrit

Efficacy parameters	End of treatment		2 week follow-up		5 week follow-up	
	Venofer (n=69)	Historical Control (n=18)	Venofer (n=73)	Historical Control (n=18)	Venofer (n=71)	Historical Control (n=15)
Hemoglobin (g/dL)	1.0±0.12 **	0.0±0.21	1.3±0.14* *	-0.6±0.24	1.2±0.17*	-0.1±0.23
Hematocrit (%)	3.1±0.37 **	-0.3±0.65	3.6±0.44* *	-1.2±0.76	3.3±0.54	0.2±0.86

**p<0.01 and *p<0.05 compared to historical control from ANCOVA analysis with baseline hemoglobin, serum ferritin and erythropoietin dose as covariates.

Serum ferritin increased significantly (p=0.0001) at endpoint of study from baseline in the Venofer®-treated population (165.3±24.2 ng/mL) compared to the historical control population (-27.6±9.5 ng/mL). Transferrin saturation also increased significantly (p=0.0016) at endpoint of study from baseline in the Venofer®-treated population (8.8±1.6%) compared to this historical control population (-5.1±4.3%) [3].

Study B: Hemodialysis Dependent Chronic Kidney Disease (HDD-CKD)
Study B was a multicenter, open label study of Venofer® (iron sucrose injection, USP) in 23 iron deficient hemodialysis patients who had been discontinued from iron dextran due to intolerance. Eligibility criteria and Venofer® administration were otherwise identical to Study A. The mean age of the patients in this study was 53 years, with ages ranging from 21-79 years. Of the 23 patients enrolled in the study, 10 (44%) were male and 13 (56%) were female. The ethnicity breakdown of patients enrolled in this study was as follows: Caucasian (35%); Black (35%); Asian (4%); Hispanic (26%). The mean change from baseline to the end of treatment (Day 24) in hemoglobin, hematocrit, and serum iron parameters was assessed.
All 23 enrolled patients were evaluated for efficacy. Statistically significant increases in mean hemoglobin (1.1±0.2 g/dL), hematocrit (3.6±0.6%), serum ferritin (266.3±30.3 ng/mL) and transferrin saturation (8.7±2.0%) were observed from baseline to end of treatment [4].

Study C: Hemodialysis Dependent Chronic Kidney Disease (HDD-CKD)
Study C was a multicenter, open-label, two period (treatment followed by observation period) study in iron deficient hemodialysis patients. Eligibility for this study included chronic hemodialysis patients with a hemoglobin less than or equal to 10 g/dL, a serum transferrin saturation less than or equal to 20%, and a serum ferritin less than or equal to 200 ng/mL, who were undergoing maintenance hemodialysis 2 to 3 times weekly. The mean age of the patients enrolled in this study was 41 years, with ages ranging from 16-70 years. Of 130 patients evaluated for efficacy in this study, 68 (52%)

were male and 62 (48%) were female. The ethnicity breakdown of patients enrolled in this study was as follows: Caucasian (23%); Black (23%); Asian (5%); Other (mixed ethnicity) (49%). Forty-eight percent of the patients had previously been treated with oral iron. Exclusion criteria were similar to those in studies A and B. Venofer®, was administered in doses of 100 mg during sequential dialysis sessions until a pre-determined (calculated) total dose of iron was administered.
Patients received Venofer® at each dialysis session, two to three times weekly. One hour after the start of each session, 5 mL iron sucrose (100 mg iron) in 100 mL 0.9% NaCl was administered into the hemodialysis line. A 50 mg dose (2.5 mL) was given to patients within two weeks of study entry. Patients were treated until they reached an individually calculated total iron dose based on baseline hemoglobin level and body weight. Twenty-seven patients (20%) were receiving erythropoietin treatment at study entry and they continued to receive the same erythropoietin dose for the duration of the study.

Changes from baseline to observation week 2 and observation week 4 (end of study) were analyzed.

The modified intention-to-treat population consisted of 131 patients. Significant ($p<0.0001$) increases from baseline in mean hemoglobin (1.7 g/dL), hematocrit (5%), serum ferritin (434.6 ng/mL), and serum transferrin saturation (14%) were observed at week 2 of the observation period and these values remained significantly increased ($p<0.0001$) at week 4 of the observation period.

Study D: Non-Dialysis-Dependent Chronic Kidney Disease (NDD-CKD)
Study D was a randomized, open-label, multicenter, active–controlled study of the safety and efficacy of oral iron versus intravenous iron sucrose (Venofer®) in NDD-CKD patients with or without erythropoietin therapy. Erythropoietin therapy was stable for 8 weeks prior to randomization. In the study 188 patients with NDD-CKD, transferrin saturation $\leq 25\%$, ferritin ≤ 300 ng/mL and an average baseline hemoglobin of ≤ 11.0 g/dL were randomized to receive oral iron (325 mg ferrous sulfate three times daily for 56 days); or Venofer® (either 200 mg over 2-5 minutes 5 times within 14 days or two 500 mg infusions on Day 1 and Day 14, administered over 3.5-4 hours). Of the 188 randomized patients, 182 were treated and followed for up to 56 days. Efficacy assessments were measured on days 14, 28, 42 and 56. The mean age of the 91 treated patients in the Venofer® group was 61.6 years, (range 25 to 86 years) and 64 years, (range 21 to 86 years) for the 91 patients in the Oral Iron group. Ethnicity breakdown of the patients in the Venofer® Group was as follows: Black (34.1%), Caucasian (60.4%), Hispanic (3.3%), Other (2.2%). Ethnicity breakdown for the Oral Iron group was: Black (44.0%), Caucasian (50.5%), Hispanic (4.4%), Other (1.1%). Patient demographic characteristics were not significantly different between the groups. A statistically significantly greater proportion of Venofer® subjects (35/79; 44.3%) compared to oral iron subjects (23/82; 28%) had an increase in hemoglobin ≥ 1 g/dL at anytime during the study ($p= 0.03$). In patients $\geq$ 65 years of age, the proportion of subjects achieving ≥ 1.0 g/dL increase in hemoglobin from baseline was 53% (20/38) in the Venofer® group compared to 23% (10/43) in the oral iron group. In patients <65 years of age, the proportion of subjects achieving ≥ 1.0 g/dL increase in hemoglobin from baseline was 37% (15/41) in the Venofer® group compared to 33% (13/39) in the oral iron group. A statistically significantly greater proportion of Venofer® treated patients (31/79; 39.2%) compared to oral iron treated patients (1/82; 1.2%) had an increase in hemoglobin ≥ 1 g/dL and ferritin ≥ 160 ng/ml at anytime during the study ($p<0.0001$).

CLINICAL INDICATIONS AND USAGE

Venofer® is indicated in the treatment of iron deficiency anemia in the following patients:

- non-dialysis dependent chronic kidney disease (NDD-CKD) patients receiving an erythropoietin
- non-dialysis dependent chronic kidney disease (NDD-CKD) patients not receiving an erythropoietin
- hemodialysis dependent chronic kidney disease (HDD-CKD) patients receiving an erythropoietin.

CONTRAINDICATIONS

The use of Venofer® is contraindicated in patients with evidence of iron overload, in patients with known hypersensitivity to Venofer® or any of its inactive components, and in patients with anemia not caused by iron deficiency.

WARNINGS

Hypersensitivity reactions have been reported with injectable iron products. See **PRECAUTIONS** and **ADVERSE REACTIONS.**

PRECAUTIONS

General:

Because body iron excretion is limited and excess tissue iron can be hazardous, caution should be exercised to withhold iron administration in the presence of evidence of tissue iron overload. Patients receiving Venofer® require periodic monitoring of hematologic and hematinic parameters (hemoglobin, hematocrit, serum ferritin and transferrin saturation). Iron therapy should be withheld in patients with evidence of iron overload. Transferrin saturation values increase rapidly after IV administration of iron sucrose; thus, serum iron values may be reliably obtained 48 hours after IV dosing. (See DOSAGE AND ADMINISTRATION and OVERDOSAGE).

Hypersensitivity Reactions:

Serious hypersensitivity reactions have been rarely reported in patients receiving Venofer®. No life-threatening hypersensitivity reactions were observed in the clinical studies. Several cases of mild or moderate hypersensitivity reactions were observed in these studies. A total of 98 anaphylactoid reactions including serious or life-threatening reactions have been reported in post-marketing spontaneous reports worldwide between 1992 and August 2004 based on estimated use in 3.4 million patients. See ADVERSE REACTIONS.

Hypotension:

Hypotension has been reported frequently in hemodialysis dependent chronic kidney disease patients receiving intravenous iron. Hypotension also has been reported in non-dialysis dependent chronic kidney disease patients receiving intravenous iron. Hypotension following administration of Venofer®

may be related to rate of administration and total dose administered. Caution should be taken to administer Venofer® according to recommended guidelines. See **DOSAGE AND ADMINISTRATION.**

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

No long-term studies in animals have been performed to evaluate the carcinogenic potential of Venofer®.

Venofer® was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y/TK+/-) forward mutation test, the human lymphocyte chromosome aberration test, or the mouse micronucleus test.

Venofer® at IV doses up to 15 mg iron/kg/day (about 1.2 times the recommended maximum human dose on a body surface area basis) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy Category B:

Teratology studies have been performed in rats at IV doses up to 13 mg iron/kg/day (about 0.5 times the recommended maximum human dose on a body surface area basis) and rabbits at IV doses up to 13 mg iron/kg/day (about 1 times the recommended maximum human dose on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to Venofer®. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers:

Venofer® is excreted in milk of rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Venofer® is administered to a nursing woman.

Pediatric Use:

Safety and effectiveness of Venofer® in pediatric patients have not been established. In a country where Venofer® is available for use in children, at a single site, five premature infants (weight less than 1,250g) developed necrotizing enterocolitis and two of the five expired during or following a period when they received Venofer®, several other medications and erythropoietin. Necrotizing enterocolitis may be a complication of prematurity in very low birth weight infants. No causal relationship to Venofer® or any other drugs could be established.

Geriatric Use:

Studies A through D did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. Of the 1,051 patients in two post-marketing safety studies of Venofer®, 40% were 65 years and older. No overall differences in safety were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Adverse Events observed in all treated populations

The frequency of adverse events associated with the use of Venofer® has been documented in five randomized clinical trials involving 231 hemodialysis dependent and 139 non-dialysis dependent patients; and in two post-marketing safety studies involving 1,051 hemodialysis dependent patients for a total of 1,421 patients. In addition, over 2,000 patients treated with Venofer have been reported in the medical literature.

Treatment-emergent adverse events reported by ≥ 2% of treated patients in the randomized clinical trials, whether or not related to Venofer® administration, are listed by indication in Table 2.

Table 2 Most Common Treatment-Emergent Adverse Events Reported in ≥ 2% of Patients By Clinical Indication (Multidose Safety Population)

Adverse Events (Preferred Term)	HDD-CKD Venofer® (N=231) %	NDD-CKD Venofer® (N=139) %	NDD-CKD Oral Iron (N=139) %
Subjects with any adverse event	78.8	76.3	73.4
Ear and Labyrinth Disorders			
Ear Pain	0	2.2	0.7
Gastrointestinal Disorders			
Abdominal pain NOS	3.5	1.4	2.9
Constipation	1.3	4.3	12.9
Diarrhea NOS	5.2	7.2	10.1
Dysgeusia	0.9	7.9	0
Nausea	14.7	8.6	12.2
Vomiting NOS	9.1	5.0	8.6
General Disorders and Administration Site Conditions			
Asthenia	2.2	0.7	2.2
Chest pain	6.1	1.4	0
Edema NOS	0.4	6.5	6.5
Fatigue	1.7	3.6	5.8
Feeling abnormal	3.0	0	0
Infusion site burning	0	3.6	0
Injection site extravasation	0	2.2	0
Injection site pain	0	2.2	0
Peripheral edema	2.6	7.2	5.0
Pyrexia	3.0	0.7	0.7
Infections and Infestations			
Nasopharyngitis	0.9	0.7	2.2
Urinary tract infection NOS	0.4	0.7	5.0
Injury, Poisoning and Procedural			

Complications			
Graft complication	9.5	1.4	0
Investigations			
Cardiac murmur NOS	0.4	2.2	2.2
Fecal occult blood positive	0	1.4	3.6
Metabolism and Nutrition Disorders			
Fluid overload	3.0	1.4	0.7
Gout	0	2.9	1.4
Hyperglycemia NOS	0	2.9	0
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	3.5	1.4	2.2
Back pain	2.2	2.2	3.6
Muscle cramp	29.4	0.7	0.7
Myalgia	0	3.6	0
Pain in extremity	5.6	4.3	0
Nervous System Disorders			
Dizziness	6.5	6.5	1.4
Headache	12.6	2.9	0.7
Respiratory, Thoracic and Mediastinal Disorders			
Cough	3.0	2.2	0.7
Dyspnea	3.5	3.6	0.7
Dyspnea exacerbated	0	2.2	0.7
Nasal congestion	0	1.4	2.2
Rhinitis allergic NOS	0	0.7	2.2
Skin and Subcutaneous Tissue Disorders			
Pruritus	3.9	2.2	4.3
Rash NOS	0.4	1.4	2.2
Vascular Disorders			
Hypertension NOS	6.5	6.5	4.3
Hypotension NOS	39.4	2.2	0.7

Treatment-emergent adverse events reported in ≥ 2% of patients by dose group are shown in Table 3.

Table 3 Most Common Treatment-Emergent Adverse Events Reported in ≥ 2% of Patients by Dose Group (Multidose Safety Population)

	HDD-CKD	NDD-CKD	
Adverse Events (Preferred Term)	**100 mg (N=231) %**	**200 mg (N=109) %**	**500 mg (N=30) %**
Subjects with any event	78.8	75.2	80.0
Ear and Labyrinth Disorders			
Ear pain	0	0.9	6.7
Gastrointestinal Disorders			
Abdominal pain NOS	3.5	1.8	0

Constipation	1.3	3.7	6.7
Diarrhea NOS	5.2	6.4	10.0
Dysgeusia	0.9	9.2	3.3
Nausea	14.7	9.2	6.7
Vomiting NOS	9.1	5.5	3.3
General Disorders and Administration Site Conditions			
Asthenia	2.2	0.9	0
Chest pain	6.1	0.9	3.3
Edema NOS	0.4	7.3	3.3
Fatigue	1.7	4.6	0
Feeling abnormal	3.0	0	0
Infusion site burning	0	3.7	3.3
Injection site pain	0	2.8	0
Peripheral edema	2.6	5.5	13.3
Pyrexia	3.0	0.9	0
Infections and Infestations			
Sinusitis NOS	0	0	3.3
Injury, Poisoning and Procedural Complications			
Graft complication	9.5	1.8	0
Investigations			
Cardiac murmur NOS	0.4	2.8	0
Metabolism and Nutrition Disorders			
Fluid overload	3.0	1.8	0
Gout	0	1.8	6.7
Hyperglycemia NOS	0	3.7	0
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	3.5	0.9	3.3
Back pain	2.2	1.8	3.3
Muscle cramp	29.4	0	3.3
Myalgia	0	2.8	6.7
Pain in extremity	5.6	4.6	3.3
Nervous System Disorders			
Dizziness	6.5	5.5	10.0
Headache	12.6	3.7	0
Respiratory, Thoracic and Mediastinal Disorders			
Cough	3.0	0.9	6.7
Dyspnea	3.5	1.8	10.0
Skin and Subcutaneous Tissue Disorders			
Pruritus	3.9	0.9	6.7
Vascular Disorders			
Hypertension NOS	6.5	6.4	6.7
Hypotension NOS	39.4	0.9	6.7

Drug related adverse events reported by ≥ 2% of Venofer® treated patients are shown by dose group in Table 4.

Table 4 Most Common Adverse Events Related to Study Drug Reported in ≥ 2% of Patients by Dose Group (Multidose Safety Population)

Adverse Events (Preferred Term)	HDD-CKD 100 mg (N=231) %	NDD-CKD 200 mg (N=109) %	NDD-CKD 500 mg (N=30) %
Subjects with any event	14.7	23.9	20.0
Gastrointestinal Disorders			
Dysgeusia	0.9	7.3	3.3
Nausea	1.7	2.8	0
General Disorders and Administration Site Conditions			
Infusion site burning	0	3.7	0
Injection site pain	0	2.8	0
Peripheral edema	0	1.8	6.7
Nervous Systems Disorders			
Dizziness	0	2.8	6.7
Headache	0	2.8	0
Vascular Disorders			
Hypotension NOS	5.2	0	6.7

Adverse Events Observed in Hemodialysis Dependent Chronic Kidney Disease (HDD-CKD) Patients

Adverse reactions, whether or not related to Venofer® administration, reported by >5% of treated patients from a total of 231 patients in HDD-CKD Studies A, B, and C were as follows: hypotension (39.4%), muscle cramps (29.4%), nausea (14.7%), headache (12.6%), graft complications (9.5%), vomiting (9.1%), dizziness (6.5%), hypertension (6.5%), chest pain (6.1%), and diarrhea (5.2%).

In the first post-marketing safety study, 665 chronic hemodialysis patients were treated with Venofer® doses of 100 mg at each dialysis session for up to 10 consecutive dialysis sessions for their iron deficiency or on a weekly basis for 10 weeks for maintenance of iron stores. In this study, 72% of the patients received up to 10 doses, 27% received between 11-30 doses, and 1% received 40 to 50 doses of Venofer®. Serious adverse events and drug-related non-serious adverse events were collected. In the second post-marketing safety study, 386 hemodialysis patients were exposed to a single dose of Venofer® (100 mg IV by slow injection over 2 minutes or 200mg IV by slow injection over 5 minutes). The mean age of patients enrolled into the two post-marketing safety studies was 59 years, with a range of 20-93 years. Males made up 60% of the population. The ethnicity of the patients enrolled in the two studies included Blacks (44%), Caucasians (41%), Asians (3%), Hispanics (11%) and others (1%). Adverse events reported by > 1% of 1051 treated patient were: cardiac failure, congestive, sepsis NOS and dysgeusia.

Adverse Events Observed in Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD) Patients

In Study D of 182 treated NDD-CKD patients, 91 were exposed to Venofer. Adverse events, whether or not related to Venofer®, reported by ≥5% of the Venofer® exposed patients were as follows: dysgeusia (7.7%), peripheral edema (7.7%), diarrhea (5.5%), constipation (5.5%), nausea (5.5%), dizziness (5.5%), and hypertension (5.5%). One serious related adverse reaction was reported (hypotension and shortness of breath not requiring hospitalization in a Venofer patient). Two patients experienced possible hypersensitivity/allergic reactions (local edema/hypotension) during the study. Of the 5 patients who prematurely discontinued the treatment phase of the study due to adverse events (2 oral iron group and 3 Venofer® group), three Venofer® patients had events that were considered drug-related (hypotension, dyspnea and nausea).

In an additional study of Venofer with varying erythropoietin doses in 96 treated NDD-CKD patients, adverse events, whether or not related to Venofer® reported by ≥5% of Venofer® exposed patients are as follows: diarrhea (16.5%), edema (16.5%), nausea (13.2%), vomiting (12.1%), arthralgia (7.7%), back pain(7.7%), headache (7.7%), hypertension (7.7%), dysgeusia (7.7%), dizziness (6.6%), extremity pain(5.5%), and injection site burning (5.5%). No patient experienced a hypersensitivity/allergic reaction during the study. Of the patients who prematurely discontinued the treatment phase of the study due to adverse events (2.1% oral iron group and 12.5% Venofer® group), only one patient (Venofer® group) had events that were considered drug-related (anxiety, headache, and nausea). Ninety-one (91) patients in this study were exposed to Venofer® either during the treatment or extended follow-up phase.

Hypersensitivity Reactions: See **WARNINGS** and **PRECAUTIONS.**
In clinical studies, several patients experienced hypersensitivity reactions presenting with wheezing, dyspnea, hypotension, rashes, or pruritus. Serious episodes of hypotension occurred in 2 patients treated with Venofer at a dose of 500mg.
From the post-marketing spontaneous reporting system, there were 98 reports of anaphylactoid reactions including patients who experienced serious or life-threatening reactions (anaphylactic shock, loss of consciousness or collapse, bronchospasm with dyspnea, or convulsion) associated with Venofer® administration between 1992 and August, 2004 based on estimated use in more than 3.4 million patients.

One hundred thirty (11%) of the 1,151 patients evaluated in the 4 U.S. trials in HDD-CKD patients (studies A, B and the two post marketing studies) had prior other intravenous iron therapy and were reported to be intolerant (defined as precluding further use of that iron product). When these patients were treated with Venofer® there were no occurrences of adverse events that precluded further use of Venofer®.

OVERDOSAGE
Dosages of Venofer® (iron sucrose injection, USP) in excess of iron needs may lead to accumulation of iron in storage sites leading to hemosiderosis. Periodic monitoring of iron parameters such as serum ferritin and transferrin saturation may assist in recognizing iron accumulation. Venofer® should not be administered to patients with iron overload and should be discontinued when serum ferritin levels

equal or exceed established guidelines [5]. Particular caution should be exercised to avoid iron overload where anemia unresponsive to treatment has been incorrectly diagnosed as iron deficiency anemia.

Symptoms associated with overdosage or infusing Venofer® too rapidly included hypotension, dyspnea, headache, vomiting, nausea, dizziness, joint aches, paresthesia, abdominal and muscle pain, edema, and cardiovascular collapse. Most symptoms have been successfully treated with IV fluids, hydrocortisone, and/or antihistamines. Infusing the solution as recommended or at a slower rate may also alleviate symptoms.

Preclinical Data:

Single IV doses of Venofer® at 150 mg iron/kg in mice (about 3 times the recommended maximum human dose on a body surface area basis) and 100 mg iron/kg in rats (about 8 times the recommended maximum human dose on a body surface area basis) were lethal.

The symptoms of acute toxicity were sedation, hypoactivity, pale eyes, and bleeding in the gastrointestinal tract and lungs.

DOSAGE AND ADMINISTRATION

The dosage of Venofer® is expressed in terms of mg of elemental iron. Each mL contains 20 mg of elemental iron.

Most CKD patients will require a minimum cumulative repletion dose of 1,000 mg of elemental iron, administered over sequential sessions, to achieve a favorable hemoglobin response and to replenish iron stores (ferritin, TSAT). Patients may continue to require therapy with Venofer® or other intravenous iron preparations at the lowest dose necessary to maintain target levels of hemoglobin, and laboratory parameters of iron storage within acceptable limits.

Administration: Venofer® must only be administered intravenously either by slow injection or by infusion.

Recommended Adult Dosage:

Hemodialysis Dependent Chronic Kidney Disease Patients (HDD-CKD): Venofer® may be administered undiluted as an 100 mg slow intravenous injection over 2 to 5 minutes or as an infusion of 100mg, diluted in a maximum of 100mL of 0.9% NaCl over a period of at least 15 minutes per consecutive hemodialysis session for a total cumulative dose of 1000 mg.

Non-Dialysis Dependent Chronic Kidney Disease Patients (NDD-CKD):

Venofer® is administered as a total cumulative dose of 1000 mg over a 14 day period as a 200 mg slow IV injection undiluted over 2 to 5 minutes on 5 different occasions within the 14 day period. There is limited experience with administration of an infusion of 500 mg of Venofer®, diluted in a maximum of 250 mL of 0.9% NaCl, over a period of 3.5-4 hours on day 1 and day 14; hypotension occurred in 2 of 30 patients treated. (See **CLINICAL TRIALS, Study D: Non-Dialysis Dependent Chronic Kidney**

Disease (NDD-CKD) Patients and **ADVERSE REACTIONS, Adverse Events Observed in Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD) Patients sections.**)

HOW SUPPLIED

Venofer® is supplied in 5 mL single dose vials. Each 5 mL vial contains 100 mg elemental iron (20 mg/mL). Contains no preservatives. Store in original carton at 25°C (77°F). Excursions permitted to 15°-30°C (59°-86°F). [See the USP controlled room temperature]. Do not freeze.

Sterile

NDC-0517-2340-01 100 mg/5 ml Single Dose Vial Individually Boxed

NDC-0517-2340-10 100 mg/5 mL Single Dose Vial Packages of 10

Rx Only

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IN2340

Rev. Luitpold Version 6/17/2005
MG #15727

AMERICAN REGENT, INC.
SHIRLEY, NY 11967

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-135 / S-008

SUMMARY REVIEW

Division Director Summary Review of a Supplemental NDA

NDA: 21-135/SE1-008
Drug: Venofer (Iron Sucrose Injection, USP)
Applicant: Luitpold Pharmaceuticals, Inc.
Date: June 18, 2004

This supplemental new drug application seeks expansion of the currently approved indication of "treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy" to "treatment of iron deficiency anemia in chronic kidney disease (CKD) patients on erythropoietin." In effect the applicant is seeking approval of an additional indication for use in the treatment of iron deficiency anemia in chronic kidney disease patients who are not on dialysis.

Medical Officer Review

The Medical Officer Review was completed by Dr. Min Lu. A single study was submitted in support of the indication. The study and its results are described below in this excerpt from Dr. Lu's review:

> Study 1VEN 99012 was a multicenter, randomized, open-label, parallel groups study of Venofer 200 mg IV weekly for 5 doses as compared to oral iron (ferrous sulfate) 325 mg three times a day for 29 days in patients with chronic kidney disease not on dialysis. Patients with creatinine clearance <40 ml/min, hemoglobin <10.5 g/dL, TSAT <25% and serum ferritin <300 ng/mL were enrolled in the study. The primary efficacy endpoints of the study were the mean changes at Day 43 from baseline in hemoglobin and ferritin levels. The differences in the mean change in hemoglobin and ferritin from baseline between the two treatment groups were tested (each was to be tested at α= 0.025).
>
> A total of 102 patients (53 patients in the Venofer group and 49 patients in the oral iron group) were randomized, 96 patients (48 patients in each group) were treated, and 82 patients (39 patients in the Venofer group and 43 patients in the oral iron group) were evaluated for primary efficacy endpoints in the study... The majority of patients were epoetin naïve (83% in the Venofer group and 90% in the oral iron group).
>
> The study failed to demonstrate that Venofer is superior to oral iron in increasing hemoglobin at Day 43 from baseline in patients with chronic kidney disease not on dialysis (1.0 mg/dL in the Venofer group and 0.7 mg/dL in the oral iron group, p= 0.14). The study showed a significant difference in an increase in ferritin level at Day 43 from baseline between the Venofer group and the oral iron group (288 ng/mL and - 5.1 ng/mL, respectively, p<0.0001). However, change in hemoglobin is a more clinically relevant and important endpoint than change in ferritin for

treatment of anemia in patients with chronic kidney disease not on dialysis since the main cause of anemia may not be iron deficiency in these patients.

The study showed significant increases in hemoglobin at Day 43 as compared to baseline in both treatment groups ($p<0.02$ in the Venofer group and $p<0.002$ in the oral iron group). Since the majority of patients were epoetin naïve and initiated epoetin treatment at the same time iron therapy was initiated in the study, an increase in hemoglobin from baseline may be due (at least in part) to new use of epoetin therapy in the both treatment groups. This was supported by an increase of hemoglobin (0.7 mg/dL) without an increase of ferritin level (- 5.1 ng/mL) in the oral iron group. In a subgroup analysis, in patients with ferritin <100 ng/ mL at baseline (20 in the Venofer group and 29 in the oral iron group) there was greater increase in hemoglobin from baseline in the Venofer group as compared to the oral iron group (1.4 g/dL and 0.9 g/dL, respectively, $p= 0.046$).

The secondary efficacy analyses had similar findings. The results showed no significant difference in an increase in hematocrit at Day 43 from baseline between the Venofer group and the oral iron group (3.7% and 2.8%, respectively, $p= 0.12$). There was a significant difference in an increase in TSAT at Day 43 from baseline between the Venofer group and the oral iron group (4.5% and 0.5%, respectively, $p< 0.0001$).

It is noteworthy that a significant proportion of randomized patients were not included in the primary efficacy analysis [26 % (14/ 53) in the Venofer group and 12% (6/ 49) in the oral iron group)]. There were 9% of patients who discontinued study before the treatment and 17% of patients who did not complete the treatment in the Venofer group as compared to 2% and 10%, respectively, in the oral iron group. These may affect the efficacy and safety results of the study.

There was a notable imbalance in the iron status at baseline between the two treatment groups. Patients with TSAT <20% and ferritin <100 ng/ mL were 33% in the Venofer group and 54% in the oral iron group. Also, there was an uneven distribution in age, gender and race between the two treatment groups.

A portion of Dr. Lu's summary of safety is provided below:

The overall incidences of treatment- emergent adverse events were similar between the Venofer group (87.5%, 42/ 48) and the oral iron group (89.6%, 43/ 48) during the treatment phase. However, patients in the Venofer group experienced more cardiovascular, endocrine, general and administration site, nervous system, and vascular disorders than in the oral iron group while patients in the oral iron group experienced more gastrointestinal (except for taste disturbance and diarrhea) and skin and subcutaneous tissue disorders than in the Venofer group. Gastrointestinal disorders were the most commonly experienced treatment-emergent adverse events in both treatment groups (47.9% in the oral iron group and 35.4% in the Venofer group). AEs that occurred more frequently

with Venofer treatment than with oral iron treatment included edema (8.3% vs. 2.1%), hyperglycemia (8.3% vs. 0%), taste disturbance (8.3% vs. 0%), dizziness (8.3% vs. 2.1%), hypertension aggravated (8.3% vs. 2.1%), and injection site burning (6.3% vs. 0%). AEs occurred more frequently with oral iron treatment than with Venofer treatment included nausea (16.7% vs. 12.5%) vomiting (12.5% vs. 8.3%), constipation (14.6% vs. 2.1%), pruritus (12.5% vs. 2.1%), abdominal pain (6.3% vs. 2.1%), weakness (6.3% vs. 0%), and nasal congestion (6.3% vs. 2.1%).

During the Extended Follow- Up Phase, at least one treatment- emergent adverse event was experienced by 78.2% (61/ 78) of the patients. The most commonly experienced treatment- emergent adverse events were diarrhea (12.8%), vomiting (9.0%), edema lower limb (9.0%), and arthralgia (9.0%).

Dr. Lu's recommendation on approvability is quoted below:

From a clinical perspective, this reviewer recommends Venofer is not approvable for the proposed indication expansion from "treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy" to "treatment of iron deficiency anemia in chronic kidney disease (CKD) patients on erythropoietin".

The clinical deficiencies include the following:

1. Only one study was conducted in patients with chronic kidney disease not on dialysis. The study failed to demonstrate that Venofer is superior to oral iron in an increase in hemoglobin at Day 43 from baseline as planned in the study protocol. The primary efficacy results showed that the difference in mean change in hemoglobin from baseline between Venofer and oral iron groups was not statistically significant (1.0 g/dL vs. 0.7 g/dL, p= 0.14).

2. Initiation of epoetin therapy in the majority of study patients (83% in the Venofer group and 90% in the oral iron group) in the study may have contributed significantly to an increase in hemoglobin at Day 43 from baseline in both treatment groups.

3. A significant proportion of randomized patients were not included in the primary efficacy analysis in the study [26 % (14/ 53) in the Venofer group and 12% (6/ 49) in the oral iron group)].

4. In the study patients in the Venofer treatment group experienced more adverse events (except for gastrointestinal disorders), serious adverse events, and premature discontinuation due to adverse events than did patients in the oral treatment group.

5. Safety information in chronic kidney disease patients not on dialysis is limited.

To resolve the clinical deficiencies, the sponsor should conduct an adequate and well-controlled study to support the efficacy and safety of Venofer for the treatment of iron deficiency in chronic kidney disease patients not on dialysis. The study should be a randomized, parallel groups controlled study. The study patients should be patients who have received epoetin therapy with a stable dose for at least 3 months before the study and who will maintain the previous epoetin dose as much as possible during the study.

Medical Team Leader Secondary Review

The Medical Team Leader, Dr. Kathy Robie-Suh concurred with Dr. Lu's recommendations. Dr. Robie-Suh's conclusions are quoted below:

The sponsor has not provided adequate support for efficacy and safety of Venofer for the indication "treatment of iron deficiency anemia in chronic kidney disease (CKD) patients on erythropoietin." The sponsor submitted a single, randomized, open-label, active controlled (oral iron), superiority study in 96 patients that failed to demonstrate superiority of Venofer over oral iron for the clinically most meaningful endpoints of increase in hemoglobin and increase in hematocrit, even though a significantly greater increase in ferritin and transferrin saturation were seen in the Venofer group and significant increases from baseline in hematologic parameters and iron indices were seen in both treatment groups. A significant design problem of the study was that the vast majority of patients in the study started both erythropoietin and iron therapy on entry into the study. Any effect of the iron treatment in either treatment group in increasing the hemoglobin and hematocrit is inextricably confounded with the probable hematopoietic effect of erythropoietin in at least some of these patients.

Venofer should not be approved for the desired indication. No labeling changes should be made at this time. Maximum Venofer dose and rate of administration should remain as in the current labeling commensurate with the experience in the hemodialysis population on erythropoietin for whom Venofer is currently labeled.

To obtain approval for the desired indication the sponsor should conduct an additional study in patients with chronic renal failure who are on a stable dose of erythropoietin at study entry to assess the effect of Venofer as compared to oral iron or other control on increase in hemoglobin and hematocrit. The study population may need to be narrowed to patients with clear evidence of significant iron deficiency.

Statistical Review and Evaluation

The statistical review was completed by Dr. Mushfiqur Rashid. Dr. Rashid reached the following conclusions:

> The evidence taken from the single study reviewed does not indicate a support for the superiority of Venofer over oral iron in increasing hemoglobin from baseline to day 43...
>
> Although the data reviewed indicates the superiority of Venofer in increasing serum ferritin for CRF patients not on hemodialysis when compared with oral iron, the control group did not have improvement at all in serum ferritin. The failure of the control group in improving serum ferritin contributed to the significant difference between the two treated groups. In fact, there was a negative change (- 5.1) of serum ferritin from baseline with a standard deviation of 36.81 in the control group. Further there appears to be baseline imbalance in serum ferritin between oral iron treated group (mean serum ferritn 103 ng/ mL) and Venofer treated group (mean serum ferritin 125 ng/ mL). The negative change in serum ferritin at Day 43 from baseline plus lower mean baseline ferritin level in the control group may have contributed toward the significant difference between the iron treated group and Venofer treated group. As a result, this single study cannot be taken as a basis of approval of Venofer 200 mg for CRF patients who are not on dialysis.
>
> The safety data showed that during the treatment phase, the overall incidence of treatment emergent adverse events for the oral iron (90%) and Venofer (88%) were comparable. Gastrointestinal disorders were the most commonly experienced treatment-emergent adverse events in both treatment groups (48% oral iron and 35% Venofer). In particular, Venofer treated patients had more cardiac disorders (25% versus 17%) and hyperglycemia NOS (8% versus 4) than the oral iron treated group. The safety data also showed that during the treatment phase, overall (at least one) drug related treatment-emergent adverse event experienced by the Venofer treated group (23%) and the oral iron treated group (40%) were comparable. Gastro-intestinal disorders were the most commonly experienced drug related treatment- emergent adverse events in both treatment groups (35% oral iron and 13% Venofer).
>
> In order to receive an approval for Venofer 200 mg, the applicant is suggested to conduct another trial with CRF patients without dialysis. The applicant may consider placebo controlled trial or adding a placebo arm along with an oral iron treated arm in the new trial.

Division of Scientific Investigations

A clinical inspection was not requested.

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/s/

Robert Justice
6/18/04 10:37:09 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-135 / S-008

OFFICE DIRECTOR MEMO

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: June 9, 2004

From: Kathy M. Robie-Suh, M.D., Ph.D.
Medical Team Leader, Hematology,
Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Subject: Medical Team Leader Secondary Review
NDA 21-135/SE1-008 Venofer (iron sucrose injection), submitted 8/15/03
Treatment of iron deficiency anemia in chronic kidney disease (CKD) patients on erythropoietin

To: NDA 21-135

Venofer is an aqueous complex of iron(III)-hydroxide in sucrose approved November 6, 2000 for use in the treatment of iron deficiency anemia in adult patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy. The approved dose is 100 mg (100 mg iron/5 mL) given by slow injection into the dialysis line over 5 minutes or 100 mg diluted into 100 mL of 0.9% NaCl and infused into the dialysis line over 15 minutes.

Venofer has been marketed in a number of countries in Europe and worldwide since 1950. Currently Venofer is marketed in 69 countries.

In the current submission the sponsor is seeking to extend the indication for Venofer to include treatment of iron deficiency anemia in chronic kidney disease (CKD) patients on erythropoietin who are not on dialysis.

To support the new indication the sponsor has submitted a single randomized, open-label study (1VEN90912) in 96 patients with chronic kidney disease (CKD) comparing Venofer to oral iron using a Venofer dosing regimen of 200 mg by intravenous injection (40 mg/min over 5 min) once weekly for 5 doses (1000 mg). Study 1VEN90912 protocol and results are described briefly below. See Medical Officer's Review by Dr. Min Lu, signed June 8, 2004 for a detailed description and review.

Study 1VEN90912 was a randomized (1:1), open-label, multi-center, active-control study in 96 patients with chronic kidney disease (CKD) (creatinine clearance <40 ml/min) comparing the effectiveness of Venofer to that of oral iron (ferrous sulfate) with regard to improvement in hemoglobin and serum ferritin. Study drug dose for Venofer was 200 mg by intravenous injection (40 mg/min over 5 min) once weekly for 5 doses (1000 mg) and dose for oral iron was 325 mg orally 3 times daily from day 1 to 29. All patients also

received erythropoietin 2,000 U subcutaneously once weekly for 6 doses. No iron was given from Day 29 until after Day 43 end-of-treatment evaluations. Efficacy was assessed by comparing the change in hematologic parameters and iron indices from baseline to day 43 between the two treatment groups. Following the end-of-treatment evaluation, patients in both treatment groups who required continued iron therapy received intravenous Venofer as needed in an Extended Followup Phase (up to Day 114) using the same dosing regimen as in the Treatment Phase. A total of 102 patients were randomized and 96 patients received study drug (48 oral iron; 48 Venofer).

Efficacy results for the intent-to-treat (ITT) population (all patients treated) during the treatment phase are shown in the table below:

1VEN90912: Change from Baseline in Efficacy Parameters (ITT)

	Oral Iron (N=48)				Venofer (N=48)				Difference in change from baseline (Venofer - oral Iron) p-value[a]
	N	BL (SD)	Change from BL (SD)	p-value	N	BL (SD)	Change from BL (SD)	p-value	
Mean Hemoglobin (g/dL):									
Day 15	45	9.8 (0.70)	0.3 (0.52)	0.002	47	9.8 (0.58)	0.3 (0.86)	0.017	
Day 36	44	9.8 (0.70)	0.6 (0.79)	<0.0001	41	9.8 (0.60)	0.7 (1.09)	<0.0001	
Day 43	43	9.7 (0.71)	0.7 (0.97)	<0.0001	39	9.9 (0.60)	1.0 (0.98)	<0.0001	0.137
Mean Ferritin (ng/mL):									
Day 15	2	40.9 (34.15)	13.6 (8.70)	0.270	5	177 (84.18)	247 (133.4)	0.014	
Day 36	45	104 (79.00)	2.8 (41.69)	0.656	42	113 (67.60)	325 (205.9)	<0.0001	
Day 43	44	104 (79.79)	-5.1 (36.81)	0.365	39	110 (66.68)	288 (163.7)	<0.0001	<0.0001
Mean Hematocrit:									
Day 15	45	30.6 (2.20)	1.0 (1.76)	<0.0001	47	31.0 (2.11)	1.5 (2.61)	<0.0001	
Day 36	44	30.6 (2.23)	2.6 (2.56)	<0.0001	41	31.0 (2.04)	2.9 (3.71)	<0.0001	
Day 42	43	30.4 (2.13)	2.8 (3.01)	<0.0001	39	31.2 (2.08)	3.7 (3.12)	<0.0001	0.1237
Mean TSAT:									
Day 15	2	15.3 (9.48)	2.7 (0.92)	0.150	5	15.0 (5.70)	1.9 (5.47)	0.484	
Day 36	45	15.3 (5.30)	2.1 (7.46)	0.069	42	16.8 (4.88)	5.1 (8.13)	<0.0001	
Day 42	44	15.3 (5.35)	0.5 (5.74)	0.567	39	16.9 (5.05)	4.5 (7.13)	<0.0001	<0.0001

SD= standard deviation; BL=baseline; TSAT=transferrin saturation
[a] value calculated using least square means

from sponsor's tables; see Medical Officer's Review (M. Lu, signed 6/8/04)

Both treatment groups showed highly statistically significant increases in hemoglobin and hematocrit from baseline to Day 43. At Day 43 about 30.2% of oral iron patients and 56.4% of Venofer patients had hemoglobin >11.0 g/dL (p=0.067). However, only the Venofer group showed a significant increase in serum ferritin and TSAT. Because most patients enrolled in the study had not received erythropoietin before the study, the effect of iron administration on change in hematologic parameters in both treatment groups

during the study is confounded with any effect of erythropoietin. (It also is not certain that any effect of erythropoietin on the hematologic parameters in this study would have been quantitatively the same in both treatment arms). The fact that in the oral iron group there was an increase in hemoglobin and hematocrit without a concurrent increase in ferritin and transferrin saturation during the study suggests that the improvement from baseline was not in large part due to iron administration. The increases in hemoglobin and hematocrit in both groups during the Treatment Phase of the study may reflect the stimulatory effect of erythropoietin on hematopoiesis in both treatment groups during the study. The fact that Venofer administration, which produced a significant increase in ferritin and transferrin saturation (TSAT), gave no greater increase in hemoglobin and hematocrit than did oral iron further supports this possibility.

Among 78 study patients who received open label Venofer 200 mg by intravenous injection once weekly from Day 43 up to Day 114 during the Extended Followup Phase, a highly significant change from baseline was seen in hemoglobin, hematocrit, ferritin and TIBC assessments taken from Day 57 to Day 114.

The sponsor conducted a secondary analysis evaluating "clinical success" defined as $\geq$0.8 g/dL change from baseline in hemoglobin and $\geq$160 ng/mL change from baseline in ferritin at any timepoint durin the treatment phase. By this analysis 62.5% (30/48) of patients in the Venofer group and 0% (0/48) of patients in the oral iron group achieved clinical success by Day 43. However, this result was driven totally by the lack of an effect of oral iron on ferritin.

Though patients in the study were anemic, the reason(s) for their anemia may have been varied and not necessarily due to iron deficiency in all patients. Study inclusion criteria required baseline hemoglobin <10.5 g/dL, TSAT <25% and serum ferritin <300 ng/mL. Baseline hemoglobin ranged from 7.5-10.7 g/dL, baseline TSAT ranged from 4.7%-28.6%, and baseline ferritin ranged from 4.2-343 ng/mL for patients in the study. Baseline ferritin was <100ng/mL in 29 (63%) oral iron patients and 20 (43%) Venofer patients. Baseline TSAT was <20% and ferritin was <100ng/mL in 26 (54.2%) oral iron patients and 16 (33.3%) Venofer patients. A summary of the efficacy results in the subpopulation having baseline ferritin <100 ng/mL is shown in the following table:

Efficacy Results (Day 43) in Patients with Ferritin <100 ng/mL at Baseline

	Oral Iron			Venofer		
	N	BL	Change from BL	N	BL	Change from BL
Mean Hemoglobin (g/dL)	28	9.7	0.9	20	9.8	1.4
Mean Ferritin (ng/mL)	29	55.9	1.6	20	52.8	217
Mean Hematocrit	28	30.4	3.1	20	31.2	4.6
Mean TSAT	29	14.1	1.3	20	16.0	5.9

reviewer's table, data from sponsor's tables, Vol. 47.19, pp. 70 through 77; see also Medical Officer's Review, M. Lu, 6/8/04, pp. 42 through 45

The pronounced greater increases in ferritin and TSAT in these severely iron deficient patients in the Venofer group as compared to the oral iron group suggest that in patients with severe iron deficiency Venofer is more effective than oral iron in repleting iron. However the difference in hemoglobin and hematocrit between the two groups is more modest. Again, the effect of the start of erythropoietin therapy at the same time as iron therapy in most of the patients in this study on the study results is not known.

Though overall proportion of patients experiencing adverse events were comparable during the Treatment Phase in both groups (Venofer 87.5%; oral iron, 89.6%), more patients in the Venofer group (14.6%) experienced serious adverse events than did patients in the oral iron group (4.2%). Also, more patients discontinued treatment due to adverse events in the Venofer group (12.5%) than in the oral iron group (2.1%). During the Extended Followup Phase about 10% of patients discontinued treatment due to adverse events. There were no cases of hypotension during the Treatment Phase; however, during the Extended Followup Phase 4 patients (5%) experienced hypotension. During the extended followup phase 11.5% of patients experienced serious adverse events. There were no reports of allergy/hypersensitivity reactions in any patients during the study. The profile of adverse events with Venofer in this study was consistent with the profile of adverse events in the current Venofer labeling.

Reviewer's comments:
The results suggest that Venofer is effective in treatment of patients with renal failure who are shown to be anemic on the basis of iron deficiency. However, this is not the population targeted in the submitted study. Many of the patients in the submitted study may have had anemia due at least partly to some cause other than iron deficiency. Indeed, improvement in hemoglobin did not correlate well with improvement in iron indices. Because most of the patients were erythropoietin naïve coming into the study and were started on erythropoietin at the same time as iron, the effect of iron on the hemoglobin and hematocrit cannot be distinguished from the effect of erythropoietin on the hemoglobin and hematocrit. The fact that there was no significant difference between the two treatment groups with regard to change in hemoglobin and hematocrit over the course of the study Treatment Phase suggests that the increase that did occur in each of the treatment groups may have been due at least in part to erythropoietin.

Also, based on Study 1VEN90912 the sponsor has proposed wording in the labeling that would increase the maximum recommended amount of Venofer to be administered per slow intravenous injection from 100 mg to 200 mg and would increase the maximum recommended rate for Venofer from 20 mg iron per minute by slow intravenous infusion to [redacted] on per minute by slow intravenous infusion in hemodialysis patients on erythropoietin for whom Venofer is already labeled. No human pharmacokinetic studies are provided to support the supplement. There is little experience with use of the dosing regimen of 200 mg per dose given at a rate of [redacted] n in these patients. In a single dose safety study where 194 hemodialysis patients received a single 200 mg dose of Venofer over 5 minutes, these patients appeared to have a higher rate of adverse events (e.g., taste peversion, diarrhea, abdominal pain, dyspnea, and pruritis) than did patients

receiving the 100 mg dose (See Medical Officer's Review, M. Lu., 5/15/03). The current submission does not contribute any additional information to the safety database for use of Venofer in hemodialysis patients on erythropoietin.

Conclusions and Recommendations:
The sponsor has not provided adequate support for efficacy and safety of Venofer for the indication "treatment of iron deficiency anemia in chronic kidney disease (CKD) patients on erythropoietin." The sponsor submitted a single, randomized, open-label, active controlled (oral iron), superiority study in 96 patients that failed to demonstrate superiority of Venofer over oral iron for the clinically most meaningful endpoints of increase in hemoglobin and increase in hematocrit, even though a significantly greater increase in ferritin and transferrin saturation were seen in the Venofer group and significant increases from baseline in hematologic parameters and iron indices were seen in both treatment groups. A significant design problem of the study was that the vast majority of patients in the study started both erythropoietin and iron therapy on entry into the study. Any effect of the iron treatment in either treatment group in increasing the hemoglobin and hematocrit is inextricably confounded with the probable hematopoietic effect of erythropoietin in at least some of these patients.

Venofer should not be approved for the desired indication. No labeling changes should be made at this time. Maximum Venofer dose and rate of administration should remain as in the current labeling commensurate with the experience in the hemodialysis population on erythropoietin for whom Venofer is currently labeled.

To obtain approval for the desired indication the sponsor should conduct an additional study in patients with chronic renal failure who are on a stable dose of erythropoietin at study entry to assess the effect of Venofer as compared to oral iron or other control on increase in hemoglobin and hematocrit. The study population may need to be narrowed to patients with clear evidence of significant iron deficiency.

cc:
NDA 21-135
HFD-180/RJustice
HFD-180/ JKorvick
HFD-180/MLu
HFD-180/KRobie-Suh
HFD-180/TClayton
HFD-180/JChoudary
HFD-180/SDoddapaneni
HFD-720/SGrosser
HFD-180/LZhou

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/s/

Kathy Robie-Suh
6/9/04 07:49:36 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-135 / S-008

MEDICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	21-135
Sponsor:	Luitpold Pharmaceuticals, Inc. One Luitpold Dr. Shirley, NY 11967
Drug name:	Venofer
Indication:	Iron Deficiency Anemia in Non-Dialysis Dependent Chronic Kidney Disease Patients
Route of Administration:	Intravenous
Submission:	SE1 008 B2 (Second Review Cycle)
Date submitted:	December 16, 2004
Review assigned:	January 15, 2005
Review completed:	May 20, 2005
Reviewer:	Andrew Dmytrijuk, M.D.

Addendum:

This is an addendum to the review dated May 20, 2005. Attached are my recommended labeling changes based on the review.

15 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Medical-*_____

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/s/

Andrew Dmytrijuk
6/16/05 04:44:27 PM
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George Shashaty
6/16/05 05:19:47 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 14, 2005

FROM: George Shashaty, M.D.
Acting Medical Team Leader, Hematology
Division of Gastrointestinal and Coagulation Drug Products
HFD-180

SUBJECT: Medical Team Leader Review
NDA 21-135 (SE1-008, dated December 16, 2004)
Venofer

TO: NDA 21-135

Background

Venofer is an aqueous complex of iron (III)-hydroxide in sucrose that was originally approved on November 6, 2000 for use in the treatment of iron deficiency anemia (IDA) in adult patients undergoing chronic hemodialysis (HD) who are receiving supplemental erythropoietin (EPO) therapy. The approved dose is 100 mg diluted in 5 ml of normal saline given slowly by injection into the dialysis line over 5 minutes, or 100 mg diluted in 100 ml of normal saline and infused into the dialysis line over 15 minutes. The drug has been available for use since 1950 and is currently marketed in 69 countries worldwide.

The current submission is a response to our letter dated June 18, 2004. That letter denied an approval for the use of Venofer for the treatment of iron deficiency anemia in patients with chronic kidney disease who were receiving erythropoietin (EPO). The non-approvability was based on the following deficiencies:

- Only a single study was submitted.
- The study failed to demonstrate that Venofer was superior to oral iron in increasing the hemoglobin at day 43 from baseline as planned in the study protocol. The difference was 1.0 g/dl compared to 0.7 g/dl, respectively ($p=0.14$).
- Initiation of erythropoietin in study patients may have contributed to the rise in hemoglobin levels in both groups of patients.
- Many of the randomized patients were not included in the primary efficacy analysis.
- Venofer treated patients experienced more adverse events, serious adverse events and discontinuation due to adverse events than patients treated with oral iron.
- Safety information for the use of Venofer in chronic kidney disease patients was limited.

In order to obtain approval for the indication, the letter stated that the sponsor would have to conduct an adequate and well controlled trial to demonstrate the efficacy and safety of the drug for the indication. In particular, it was believed important that patients should have been on a stable dose of erythropoietin prior to, and then during, the initiation of iron therapy.

In the current submission, the sponsor responds to the non-approval letter by providing results of a new study (1VEN03027). This study is intended to support the indication of the use of Venofer in patients with chronic kidney disease not requiring dialysis who have iron deficiency anemia and are receiving a stable dose (or no) EPO. The primary medical review was performed by Dr. Andrew Dmytrijuk and is dated June 10, 2005.

Review of the Submission

Study 1VEN03027 was an open-label, phase III, randomized, active-controlled, multi-institutional trial in which patients with chronic renal insufficiency (creatinine clearance <60 ml/min/1.73m^2) who were receiving a stable dose of EPO (including zero EPO) for 8 weeks prior to study drug therapy were treated with either intravenous Venofer or orally administered ferrous sulfate. Entry into the trial required a hemoglobin (Hgb) level of ≤11.0 g/dl, a transferrin saturation (TSAT) ≤25% and a serum ferritin ≤300 ng/ml. Exclusion criteria included other chronic diseases, the recent need for blood transfusion, known bleeding, pregnancy, and alcohol or drug abuse. Venofer was administered as 1000 mg in divided intravenous doses over a 14 day period, either as a 200 mg slow injection over 5 minutes (40 mg/min) for 5 doses or as a 500 mg infusion given over 3.5-4.0 hours (2 mg/min) on days 0 and 14 (after Aug 24, 2004, all subjects weighing less than 70 kg who were given the 500 mg dose were to have the infusion given over a 5 hour period because of hypotension that had occurred in relation with the 4 hour infusion in 2 subjects with a weight below 70 kg). Oral iron was administered three times daily at a dose of 325 mg tablets (65 mg elemental iron) for 56 days.

After stratification by gender, Hgb level and use/non-use of EPO, subjects were randomized at a 1:1 ratio to either Venofer or oral iron. Subjects were followed at 2 week intervals through day 56 with blood counts, measures of serum iron levels and safety evaluations.

The primary efficacy endpoint was the proportion of subjects in the ITT population in each treatment arm who had an increase in Hgb of ≥1.0 g/dl at any time between baseline and the end of the study or time of intervention (defined as an increase in the dose of EPO, administration of a blood transfusion or use of iron outside the protocol). Multiple secondary endpoints were also evaluated.

One hundred and eighty two (182) subjects were treated in the trial. However, only 161 were included in the intent-to-treat population, virtually entirely because after randomization and prior to the administration of study drug, a stable EPO dose could not be established. Therefore, in the ITT population, 79 were treated in the Venofer arm and 82 were treated in the oral iron arm. Demographic characteristics of persons in the two arms of the trial were generally similar, although those in the oral iron arm were somewhat older (median age, 66 vs. 63), more often

black (44% vs. 34%), and were more likely to have a creatinine clearance ≤30 ml/min (67% vs. 57%). The degree of compliance with the therapeutic regimen was greater in the Venofer arm compared to the oral iron arm (97% vs. 83%).

A greater proportion of Venofer treated subjects compared to oral iron treated subjects reached the primary efficacy endpoint of an increase in Hgb ≥1.0 gm/dl at some time during the 56 day length of the trial (44.3%, 35/79 vs. 28%, 23/82) (p=0.034).

Achievement of the primary efficacy endpoint was consistent across subgroups varying by age, sex, race, level of Hgb at entry into the trial, EPO use or level of creatinine clearance. The size of the subgroups was small and limited statistical inference. The degree of compliance with the therapeutic regimen did not affect the outcome.

The administration of Venofer was associated with an increase of serum ferritin in the majority of patients, whereas almost no patients treated with oral iron had a rise in serum ferritin. TSAT increased in the majority of subjects in both arms of the trial.

Safety assessment was performed on all subjects who received at least one dose of study drug. Included in the safety assessment were 91 subjects in each arm.

No deaths occurred during the study period.

Serious adverse events (AE)s developed in 11% of subjects in the Venofer treated arm. These included fluid overload, flank pain, angina, hypotension, dyspnea, pleural effusion, intraoperative hemorrhage, hyponatremia, mental status changes, respiratory failure, pneumonia and acute renal failure. Of these, only hypotension and dyspnea occurring in the same patient were believed to be study drug related. Serious AEs developed in 6.6% of subjects in the oral iron treated arm. These included fluid overload, hip fracture (2), syncope, pneumonia and fracture reduction. Neither of these SAEs were believed to be study drug related.

Premature discontinuation of study drug due to AEs believed to be related to study drug occurred in 3 subjects in the Venofer treated arm. These included hypotension in 2 subjects, dyspnea, nausea and local skin swelling. Some of these reactions were thought to be related to hypersensitivity to the study drug. Hypotension was thought to be related to the too rapid administration of Venofer in underweight (<70 kg) individuals. Premature discontinuation of study drug due to AEs believed to be related to study drug occurred in 2 subjects in the oral iron treated arm. Both SAEs were hip fractures and were thought not to be related to study drug.

Although the frequency and intensity (most were mild or moderate) of treatment-emergent AEs was similar between the two arms of the trial (70% for Venofer, 65% for oral iron), there was a difference in the types of AEs between the two groups. In the Venofer treated arm, the most common AEs included dysgeusia (7.7%), peripheral edema (7.7%), constipation (5.5%), diarrhea (5.5%), dizziness (5.5%), hypertension (5.5%) and nausea (5.5%). In the oral iron treated group, the most common AEs were constipation (12.1%), diarrhea (9.9%), nausea (9.9%), edema (8.8%), fatigue (6.6%), vomiting (6.6%), urinary tract infection (6.6%) and stool positive for

occult blood (5.5%). AEs believed to be drug related and different in frequency between the 2 arms of the trial included gastrointestinal symptoms of constipation, nausea, and diarrhea in 17.6% of the oral iron treated group compared to 8.8% in the Venofer treated group. In contrast, study drug related dysgeusia developed in 5.5% of Venofer treated subjects but in none of the oral iron treated subjects.

The statistical analysis of the primary endpoint was the unstratified comparison of the Hgb response rate between the 2 study groups using a 2-sided Fisher's exact test at the 0.05 significance level. The p value for the comparison for this analysis was 0.034.

The statistical review of the submission (Mushfiqur Rashid, Ph.D. and Stella Grosser, Ph.D., dated May 19, 2005) concluded that "The current submission also does not provide statistically persuasive results (p-value 0.03 by primary analysis; p-value 0.05 by logistic regression analysis; p-value 0.16 of Cochran-Mantel-Haenszel test) with respect to the primary endpoint (Percent of subjects with $\geq$ 1.0 g/dL hemoglobin increase from baseline) when considered as a single study. However, this is an active control study with oral iron as a comparator. The oral iron has an effect of increasing hemoglobin in general. The medical review should address this issue in depth". The statistical review for safety indicated that "the incidence of any specific treatment related adverse events was comparable between the two groups except the incidence of gastro-intestinal disorders (9% Venofer and 18% oral iron)".

There was no new CMC, toxicology or biopharmacology data submitted with the application.

Conclusions

The sponsor has submitted a new study in response to our non-approvable letter of June 18, 2004. The study has addressed most of the deficiencies delineated in the non-approvable letter, most particularly in comparing the proportion of respondents with a clinically meaningful increase in Hgb as the primary efficacy endpoint (rather than the mean rise in hemoglobin) and in the establishment and maintenance of a stable dose of EPO prior to and during the trial. In addition, the study provides for an increase in the evaluable safety population.

The following deficiencies were not resolved:

- Only a single study was provided in support of the indication.
- The difference in the number of randomized patients not included in the efficacy (ITT) population (16/95 in the Venofer treated arm, 11/93 in the oral iron treated arm) remains large, although the proportional difference has been reduced by an increase in the number of subjects recruited into the trial.
- Venofer treated subjects continued to have more SAEs and discontinuations due to AEs than did oral iron treated subjects.

Study 1VEN03027 does provide evidence that the administration of intravenous Venofer to persons with non-dialysis dependent chronic kidney disease with iron deficiency anemia increases the Hgb by $\geq$1 gm/dl in a statistically significantly greater proportion of such persons

when compared to the oral administration of iron given for the same purpose. This effect is seen whether or not the patient is receiving EPO as a red cell stimulant.
The sponsor has submitted only a single study for the indication, and the statistical review indicates that the study does not provide "persuasive" results for efficacy. Nonetheless, the sponsor has conducted several trials in similar medical conditions that led to approval of the drug for use in patients with dialysis dependent chronic kidney disease with iron deficiency anemia receiving EPO. Although dialysis is more likely to cause iron deficiency because of the loss of red cells during the dialysis procedure and because of a higher incidence of gastrointestinal blood loss in azotemic patients, the common feature of diminished EPO secretion by diseased kidneys, and its replacement exogenously, does seem able to provoke relative iron deficiency in a stimulated marrow. Therefore, it seems reasonable to conclude that the trials upon which the original approval for the indication was based lend support to the new indication.

The major safety concern raised in the study is the development of hypotension and possible other manifestations of anaphylaxis/hypersensitivity (local edema, dyspnea). The sponsor believes that such reactions are due to the dose and the relative rate of infusion of Venofer, and recommends that the length of the infusion in patients receiving the 500 mg dose be extended to 5 (rather than 3.5-4 hours). There were only 30 patients in the trial who received the 500 mg dose, and this number is insufficient to warrant a statement suggesting that the 500 mg dose can be safely administered to anyone.

Recommendations

Venofer should be approved for the treatment of iron deficiency anemia in patients with non-dialysis dependent chronic kidney disease who are or are not receiving EPO concomitantly. This approval is based on agreement on revisions to the sponsor's proposed labeling, most importantly referring to:

- The elimination of the sponsor's study D. That study can be used only for safety data.
- A clearer statement of the possibility of hypotensive/hypersensitivity events when the 500 mg infusion is administered.
- A removal of the use of Venofer as a drug to maintain optimal body stores of iron.
- References to the study of Venofer in patients _____ should be removed.

Pediatric studies for safety/efficacy and PK/PD should be performed to comply with PREA. These studies may be deferred until 2010.

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/s/

George Shashaty
6/17/05 05:05:49 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	21-135
Sponsor:	Luitpold Pharmaceuticals, Inc. One Luitpold Dr. Shirley, NY 11967
Drug name:	Venofer
Indication:	Iron Deficiency Anemia in Non-Dialysis Dependent Chronic Kidney Disease Patients
Route of Administration:	Intravenous
Submission:	SE1 008 B2 (Second Review Cycle)
Date submitted:	December 16, 2004
Review assigned:	January 15, 2005
Review completed:	May 20, 2005
Reviewer:	Andrew Dmytrijuk, M.D.

I. Background

The management of anemia in chronic kidney disease (CKD) patients has undergone significant changes with the approval of erythropoietin (EPO) products and intravenous iron (Fe) preparations. Current Kidney/Dialysis Outreach Quality Initiative (K/DOQI) guidelines for the treatment of anemia in CKD state that supplemental Fe should be administered to prevent Fe deficiency and to maintain adequate Fe stores so that CKD patients can achieve and maintain a hemoglobin (Hgb) of 11 to 12 g/dl in conjunction with EPO therapy. The guidelines further state that if oral Fe is given, it should be administered at a daily dose of at least 200mg of elemental Fe for adults. Adult CKD patients may not be able to maintain adequate Fe status with oral (po) Fe. Therefore, 500 to 1000 mg of Fe dextran may be administered intravenously (IV) in a single infusion, and repeated as needed after an initial one-time test dose of 25 mg.

The 2000 K/DOQI guidelines further recommend that the therapeutic targets for Fe therapy be a TSAT of $\geq$ 20% and a serum ferritin level of $\geq$ 100ng/ml as some studies show that TSAT < 20% and ferritin < 100ng/ml are indicative of Fe deficiency. In addition to patients who demonstrate the findings of Fe deficiency on their initial in evaluation, a number of patients demonstrate declining TSAT despite normal ferritin levels once they have begun EPO therapy. These patients are termed functionally Fe deficient, and they may benefit from IV Fe therapy. Some studies, in otherwise normal patients, indicate that Fe deficiency is considered "absolute" when Fe stores are depleted, as indicated by serum ferritin levels <12 ng/mL, and Fe delivery to the erythroid marrow is impaired, as evidenced by TSAT levels below 16%. Absolute Fe deficiency in CKD patients has been defined as serum ferritin levels <100 ng/mL and TSAT levels <20%. In contrast to absolute Fe deficiency, functional Fe deficiency results when there is a need for a greater amount of Fe to support hemoglobin synthesis than can be released from Fe stores (reticuloendothelial cells). This situation, which can be caused by pharmacological stimulation of erythropoiesis by EPO, can occur in the presence of adequate Fe stores. As a result, the percent TSAT decreases to levels consistent with Fe deficiency despite a normal or elevated serum ferritin. Patients with this condition do not meet traditional laboratory criteria for absolute Fe deficiency, but may demonstrate an increase in Hgb/Hct when IV Fe is administered.[1]

Venofer is an aqueous complex of iron(III)-hydroxide in sucrose that was approved on November 6, 2000 for use in the treatment of iron deficiency anemia (FeDA) in adult patients undergoing chronic hemodialysis (HD) who are receiving supplemental EPO therapy. The approved dose is 100 mg (100mg/5ml) given by slow injection into the dialysis line over 5 minutes or 100 mg diluted into 100 ml of 0.9% NaCl and infused into the dialysis line over 15 minutes.

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[1] Eschbach, J.W. et al.: National Kidney Foundation Kidney/Disease Outcome Quality Initiative Guidelines 2000. Website:
http://www.kidney.org/professionals/kdoqi/guidelines_updates/doqi_upex.html#an.

Venofer has been available since 1950 and is currently marketed in 69 countries worldwide. In the current submission the sponsor is seeking to extend the indication for Venofer to include treatment of FeDA in CKD patients on EPO who do not require HD. The sponsor submitted a single study, 1VEN99012 on August 15, 2003(NDA 21-135 SE1-008), in support of this proposed indication. The review of the sNDA was completed on May 17, 2004 by Dr. Min Lu. 1VEN99012 was a multicenter, randomized (1:1), open-label, parallel group active-control study of Venofer 200 mg IV weekly for 5 doses as compared to oral Fe given as ferrous sulfate (FeSO4) 325mg three times a day (tid) for 29 days in patients with CKD not on HD. Patients with a creatinine clearance (CrCL) < 40 ml/min, Hgb < 10.5 g/dl, transferrin saturation (TSAT) <25% and serum ferritin < 300 ng/ml were enrolled in the study. The primary efficacy endpoints of the study were the change in mean Hgb and in serum ferritin from baseline to day 43. The differences in the mean change in Hgb and ferritin from baseline between the 2 treatment groups were tested at $\alpha = 0.025$.

A total of 102 patients (53 in the Venofer arm and 49 in the FeSO4 arm) were randomized, 96 patients (48 in each group) were treated and 82 patients (39 in the Venofer group and 43 in the FeSO4 group were evaluated for the primary efficacy endpoints in the study. The majority of patients were EPO naïve (83% in the Venofer group and 90% in the po FeSO4 group). However, all patients received 2000 U of subcutaneous (sc) EPO once weekly (qweek) for 6 doses. No iron was given from day 29 until after day 43 (end-of-treatment evaluation).

The study failed to demonstrate that Venofer was superior to oral Fe in increasing the mean Hgb at day 43 from baseline in patients with CKD not on HD (1.0mg/dl in the Venofer group and 0.7mg/dl in the FeSO4 group, $p = 0.14$). The study showed a significant difference in the increase in ferritin level at day 43 from baseline between the 2 groups (288ng/ml in the Venofer group versus -5.1ng/ml in the FeSO4 group, $p < 0.0001$). Dr. Lu stated that Hgb is a more clinically relevant and important endpoint than a change in ferritin for treatment of anemia in patients with CKD not on HD and that the main cause of anemia in these patients might not be Fe deficiency. The study showed significant increases in Hgb at day 43 as compared to baseline in both treatment groups. At day 43, 56.4% of Venofer treated and 30.2% of FeSO4 treated patients had Hgb >11g/dl ($p=0.067$). Since the majority of patients were EPO naïve and initiated EPO at the same time as Fe therapy, an increase in Hgb from baseline might have been due to EPO therapy in both treatment groups. This conclusion was supported by the fact that there was an increase in Hgb without an increase of ferritin in the FeSO4 group. In a subgroup analysis, in patients with ferritin < 100ng/ml at baseline (20 in the Venofer group and 29 in the FeSO4 group there was a greater increase in Hgb from baseline in the Venofer group as compared to the po FeSO4 group (1.4g/dl and 0.9g/dl respectively, $p=0.046$).

Secondary efficacy analyses showed similar results. There was no significant difference in the increase in hematocrit (Hct) at day 43 from baseline between the

Venofer group and the FeSO4 group (3.7% and 2.8% respectively, p=0.12). There was a significant difference in the increase in TSAT at day 43 from baseline between the Venofer group and the FeSO4 group (4.5% and 0.5% respectively, p<0.0001).

Dr. Lu noted that there was a large number of randomized patients that were not included in the primary efficacy analysis in the Venofer group and FeSO4 group (26.4% and 12.2% respectively). Nine percent of patients randomized to the Venofer arm were not treated with Venofer compared to 2% randomized to the FeSO4 arm who were not treated with oral Fe. Seventeen percent of patients did not complete treatment in the Venofer group compared to 10% in the FeSO4 group. These dropout rates may have affected the efficacy and safety results of the study.

The measured iron status at baseline was considerably lower in the FeSO4 treated patients. Thirty three percent of patients in the Venofer group and 54% in the FeSO4 group had a TSAT <20% and ferritin <100ng/ml at study entry.

The results of study 1VEN90912 for the intention-to-treat (ITT) population are shown in the table below.

1VEN90912: Change from Baseline in Efficacy Parameters (ITT)

	Oral Iron (N=48)				Venofer (N=48)				Difference in change from baseline (Venofer - oral Iron) p-value[a]
	N	BL (SD)	Change from BL (SD)	p-value	N	BL (SD)	Change from BL (SD)	p-value	
Mean Hemoglobin (g/dL):									
Day 15	45	9.8 (0.70)	0.3 (0.52)	0.002	47	9.8 (0.58)	0.3 (0.86)	0.017	
Day 36	44	9.8 (0.70)	0.6 (0.79)	<0.0001	41	9.8 (0.60)	0.7 (1.09)	<0.0001	
Day 43	43	9.7 (0.71)	0.7 (0.97)	<0.0001	39	9.9 (0.60)	1.0 (0.98)	<0.0001	0.137
Mean Ferritin (ng/mL):									
Day 15	2	40.9 (34.15)	13.6 (8.70)	0.270	5	177 (84.18)	247 (133.4)	0.014	
Day 36	45	104 (79.00)	2.8 (41.69)	0.656	42	113 (67.60)	325 (205.9)	<0.0001	
Day 43	44	104 (79.79)	-5.1 (36.81)	0.365	39	110 (66.68)	288 (163.7)	<0.0001	<0.0001
Mean Hematocrit:									
Day 15	45	30.6 (2.20)	1.0 (1.76)	<0.0001	47	31.0 (2.11)	1.5 (2.61)	<0.0001	
Day 36	44	30.6 (2.23)	2.6 (2.56)	<0.0001	41	31.0 (2.04)	2.9 (3.71)	<0.0001	
Day 42	43	30.4 (2.13)	2.8 (3.01)	<0.0001	39	31.2 (2.08)	3.7 (3.12)	<0.0001	0.1237
Mean TSAT:									
Day 15	2	15.3 (9.48)	2.7 (0.92)	0.150	5	15.0 (5.70)	1.9 (5.47)	0.484	
Day 36	45	15.3 (5.30)	2.1 (7.46)	0.069	42	16.8 (4.88)	5.1 (8.13)	<0.0001	
Day 42	44	15.3 (5.35)	0.5 (5.74)	0.567	39	16.9 (5.05)	4.5 (7.13)	<0.0001	<0.0001

SD= standard deviation; BL=baseline; TSAT=transferrin saturation
[a] value calculated using least square means

from sponsor's tables; see Medical Officer's Review (M. Lu, signed 6/8/04)

In the review of safety, Dr. Lu noted that the overall incidences of treatment emergent adverse events were similar between the Venofer group (42/48) and the FeSO4 group (43/48) during the treatment phase. However, patients in the Venofer group had more cardiovascular, endocrine, general and administration

site, nervous system and vascular disorders than in the FeSO4 group. Patients in the FeSO4 group had more gastrointestinal and skin disorders than in the Venofer group. Gastrointestinal disorders were the most commonly experienced treatment-emergent adverse events in both treatment groups (47.9% in the FeSO4 group compared to 35.4% in the Venofer group. Adverse events that occurred more frequently with Venofer treatment than with FeSO4 treatment included edema (8.3% compared to 2.1%), hyperglycemia (8.3% compared to 0%), taste disturbance (8.3% compared to 0%), dizziness (8.3% compared to 2.1%), aggravated hypertension (8.3% compared to 2.1%) and injection site burning (6.3% compared to 0%). Adverse events occurred that occurred more frequently with FeSO4 treatment compared to Venofer treatment were nausea (16.7% compared to 12.5%), vomiting (12.5% compared to 8.3%), constipation (14.6% compared to 2.1%, pruritis (12.5% compared to 2.1%) abdominal pain (6.3% compared to 2.1%), weakness (6.3% compared to 0%) and nasal congestion (6,3% compared to 2.1%).

During the extended follow-up phase of the study, at least one treatment emergent adverse event was experienced by 61/78 of the patients. The most commonly experienced treatment emergent adverse events were diarrhea (12.8%), vomiting (9.0%), edema of the lower limb (9.0%) and arthralgia (9.0%).

Based on these results from 1VEN99012 Dr. Lu recommended that Venofer not be approved for the proposed indication of treatment of FeDA in patients undergoing chronic HD who are receiving supplemental EPO therapy. The clinical deficiencies cited were as follows:

- Only one study was conducted in patients with CKD not on HD. The study failed to demonstrate that Venofer was superior to FeSO4 in its ability to increase Hgb at day 43 from baseline as planned in the study protocol. The primary efficacy results showed that the difference in the mean change in Hgb from baseline between Venofer and FeSO4 groups was not statistically significant (1.0g/dl compared to 0.7g/dl respectively, p=0.14).
- Initiation of EPO therapy in the majority of study patients (83% in the Venofer group and 90% in the FeSO4 group) may have contributed significantly to the increase in Hgb at day 43 compared to baseline in both treatment groups.
- A significant portion of randomized patients were not included in the primary efficacy analysis in the study (14/53 in the Venofer group compared to 6/49 in the FeSO4 group).
- In 1VEN99012, the Venofer group experienced more adverse events (except for gastrointestinal disorders), serious adverse events and premature discontinuation due to adverse events than did patients in the FeSO4 group.
- Safety information for Venofer in CKD patients not on HD is limited.

The sponsor was informed that to resolve the clinical deficiencies, another adequate and well controlled study to support the efficacy and safety of Venofer for the treatment of FeDA in CKD patients not on HD would be needed. It was also recommended that patients should be on stable doses of EPO for at least 3 months before entry into the study and should maintain the previous EPO dose as much as possible during the study.

In order to address the concerns listed above, the sponsor has submitted study **1VEN03027 ("Comparison of the Safety** and Efficacy of Intravenous Iron versus Oral Iron in Chronic Renal Fa**ilure Subjects with Anemia").**

II. Study

Objectives

The primary objective of 1VEN03027 was to assess the comparative efficacy of 2 forms of Fe therapy (parenterally administered Venofer and po FeSO4) independent of hemoglobin response to EPO. EPO was to be started and maintained at a stable dose for at least 8 weeks to maximize its effect before Fe therapy was initiated. Subjects not receiving EPO at the time of entry into the study were considered to have an EPO dose of zero.

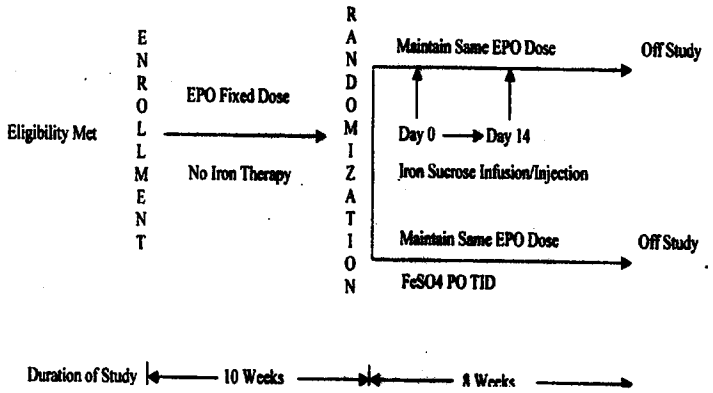
Design

1VEN03027 was an open-label, Phase III, randomized, active-control multi-institutional study. Anemic CKD patients with a diagnosis of renal insufficiency (defined as either kidney damage or glomerular filtration rate < 60ml/min/1.73m^2 for > 3months with kidney damage defined as pathologic abnormalities or markers of damage including abnormalities in blood tests, urine tests or imaging studies) who required Fe supplementation, fulfilled all the inclusion and exclusion criteria (see below), and had given informed consent were enrolled. The duration of the study for each subject was a maximum of 18 weeks. Subjects were screened for study entrance eligibility and then followed in an enrollment phase for a maximum of 10 weeks. Once a subject met the criteria for randomization, including a Hgb ≤ 11 g/dl, TSAT ≤ 25%, ferritin ≤ 300 ng/ml and a stable dose of EPO for eight weeks they were randomized into the study.

After randomization, subjects were stratified by gender, Hgb (≤ 9.0 g/dl, 9.1-10.0 g/dl, 10.1-11.0 g/dl) and current use of EPO. Subjects were then randomly assigned to either Venofer (500 mg IV infusion on days zero and 14 or 200 mg injections on five different occasions from day 0 to day 14) or oral FeSO4 (325 mg PO tid for 56 days). These doses reflect K/DOQI 2000 recommendations for the treatment of FeDA. The EPO dose was to remain fixed except for dosage reductions for safety reasons. Assessments for efficacy including complete blood count (CBC), Fe indices and safety were performed every 2 weeks following the

first dose of study drug through day 56. Subjects were randomized in a 1: 1 ratio between the treatment arms.

The diagram below shows the study design.



The table below shows the schedule of evaluations and laboratory parameters for the study. A Hgb value of ≤ 11.5 g/dl was required for inclusion in the enrollment phase of the study. A Hgb value of ≤ 11.0 g/dl, based on the average of 2 laboratory values drawn on different days within a 7-day period was required for inclusion in the randomization phase of the study. This confirmatory Hgb had to have a difference < 0.5g/dl from the qualifying Hgb and was the baseline Hgb.

Table 3.5a Schedule of Evaluations

	Enrollment				Treatment				
Visit Number	1	2	3	4	1	2	3	4	5
Day from Randomization[a]	Week -10 (max. -70 days)	Week -6 (max. -42 days)	Week -2 (max. -7 days)	Week -1 (max. -7 days)	0	14	28	42	56
Informed consent	X								
Medical history	X								
Basic Physical exam[b]					X				X
Vital signs[b,d]					X	X			
Weight[b]	X	X	X			X	X	X	
Clinical Chemistry	X								X
Hematologic Parameters	X	X	X	X[e]		X	X	X	X
Iron Indices	X	X	X			X	X	X	X
C-reactive protein	X	X	X			X	X	X	X
Stool Guaiac	X	X	X		X	X	X	X	X
Pregnancy test	X								
Concomitant Medications	X	X	X		X	X	X	X	X
Adverse event assessment		X	X		X	X	X	X	X
Quality of Life Assessment					X				X
Venofer® dosing[c,d]					A	A			
Dispensed $FeSO_4$					B	B	B	B	

A = Treatment Group A; B = Treatment Group B

a Subjects were eligible for randomization once they met all criteria for randomization.

b Physical Exam included recording of vital signs and weight.

c Venofer® 1000 mg IV in divided doses over a 14-day period as either: 500 mg infusion over 3.5-4 hours on Days 0 and 14 in 250 cc Normal Sterile Saline or 200 mg injection (undiluted) over 2-5 minutes on 5 different occasions within the 14-day period. After 24 August 2004, all subjects weighing < 70 kg who were to receive the 500 mg dose were to have the infusion time increased to 5 hours for both the first and second infusions.

d Vital signs on Venofer® dosing days were performed prior to the infusion, during the infusion, and 20 minutes post-infusion for subjects who received the 500 mg doses and prior to the injection and 20 minutes post-injection for subjects who received the 200 mg doses.

e Confirmatory hemoglobin only.

The table below shows the toxicity criteria used for this study.

Table 3.5b NIH/CTC Toxicity Criteria Examples

Adverse Event	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Allergic reaction/ hypersensitivity (including drug fever)	None	Transient rash, drug fever < 38 °C (< 100.4 °F)	Urticaria, drug fever ≥ 38 °C (≥ 100.4 °F), and/or asymptomatic bronchospasm	Symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema	Anaphylaxis
Hypotension	None	Changes, but not requiring therapy (including transient orthostatic hypotension)	Requiring brief fluid replacement or other therapy, but not hospitalization; no physiologic consequences	Requiring therapy and sustained medical attention, but resolves without persisting physiologic consequences	Shock (associated with acidemia and impairing vital organ function due to tissue hypo-perfusion)
Urticaria (hives, welts, wheals)	None	Requiring no medication	Requiring PO or topical treatment or IV medication or steroid for < 24 hours	Requiring IV medication or steroids for ≥ 24 hours	

If a CTC criterion did not exist, the Investigator was to have used the grade or adjectives as defined in Table 3.5c.

The table below shows the grading scale for adverse events used during this study.

Table 3.5c Grading of Adverse Event Severity

Grade	Adjective	Description
1	Mild	Did not interfere with subject's usual function
2	Moderate	Interfered to some extent with subject's usual function
3	Severe	Interfered significantly with subject's usual function
4	Life-Threatening	Resulted in a threat to life or in an incapacitating disability

The Investigator was asked to document his/her opinion of the relationship of the event to the study drug as follows:

- **None** - the event could be readily explained by the subject's underlying medical condition or concomitant therapy and no relationship existed between the study drug and the event. In this event, an alternative etiology was to be indicated.
- **Unlikely** - the temporal relationship between the event and the administration of the study drug was uncertain and it was likely that the event could be explained by the subject's medical condition or other therapies.
- **Possible** - there was some temporal relationship between the event and the administration of the study drug and the event was unlikely to be explained by the subject's medical condition or other therapies.

Patients

The inclusion criteria for the enrollment phase of the study were as follows:

- Male or female CKD patients over the age of 18 and able to give informed consent.
- Diagnosis of renal insufficiency based on a measured decreased CrCL.
- Hgb ≤ 11.5 g/dl (based on local laboratory value).
- Anemia secondary to renal insufficiency.

The exclusion criteria for the enrollment phase of the study were as follows:

- Known sensitivity to any component of Venofer or FeSO4.
- Chronic or serious infection, malignancy or major surgery in the month prior to enrollment.
- Parenteral iron in the past 6 months.
- Blood transfusion within the 2 months prior to enrollment.
- Significant blood loss within the past 3 months. Subjects with positive guaiac results required investigator evaluation and approval for study entry.
- Concomitant severe diseases of the liver, cardiovascular system, severe psychiatric disorders or other conditions which, in the opinion of the investigator made participation on acceptable.
- Pregnant or lactating women.
- Currently been treated for asthma.
- Anticipated surgery requiring hospitalization during the study other than vascular access or peritoneal catheterization surgery.
- Anticipated dialysis or renal transplant during the study.
- Received an investigational drug within 30 days of enrollment.
- Chronic alcohol or drug abuse within the past 6 months.
- Hemochromatosis or hemosiderosis.

A subject was eligible for randomization once he/she met the following criteria:

- Hgb $\leq$ 11.0 g/dl, based on the average of two laboratory values drawn on different days within a 7 day period prior to randomization. The difference between the 2 laboratory values could not exceed 0.5 g/dl.
- TSAT $\leq$ 25%.
- Ferritin $\leq$ 300 ng/ml.
- Stable or no EPO use for 8 weeks.
- No other Fe than study drug following enrollment.
- Continued to meet all non-laboratory inclusion and exclusion criteria.

A subject who wished to withdraw from the study could have done so at any time without the need to justify their decision. The investigator could withdraw a subject from the trial at any time if he/she felt it was in the best interest of the subject. The investigator could also withdraw the subject for any of the following reasons:

- Intervention requiring blood transfusion, any increase in EPO or Fe administration.
- Renal transplant.
- Required dialysis.
- Occurrence of an infection with ferritin > 500 ng/ml.

Subjects who were withdrawn for the above listed reasons were to be replaced. At the time of the withdrawal, procedures for the day 56 visit were performed regardless of whether the subject had completed study drug treatment.

The table below shows the number of subjects planned, randomized and treated along with the number of patients that were in the ITT population and safety population.

Number of Subjects Planned, Randomized and Treated*		
	Venofer	FeSO4
Planned	80	80
Randomized	95	93
Treated	91	91
Intent-to-Treat population (ITT)	79	82
Safety Population	91	91
Subjects Discontinued from study	21	19
Reasons for Discontinuation:		
• Adverse Event	4	2
• Required HD	3	3
• Selection Criteria/Compliance	2	0
• Lost to Follow-Up	0	2
• Subject Request	4	2
• Other	0	2
• Subjects requiring intervention	8	8
Subjects Who Completed Study	70	72

*Table derived from sponsor's table 5.1a and table on page 3.

In this study, 188 subjects at 35 centers were randomized to receive Venofer or FeSO4. Of these 188 subjects, 4 patients who were randomized to Venofer and 2 patients who were randomized to FeS04 were discontinued from the study prior to dosing. Of the 4 subjects who were randomized to Venofer, 2 patients were lost to follow-up and 2 were discontinued due to subject request. Of the 2 subjects who were randomized to FeS04, 1 discontinued due to subject request and one discontinued due to an intervention (received a blood transfusion). These six subjects were excluded from the population of subjects evaluated for efficacy and safety. Therefore, a total of 91 subjects were assigned to the Venofer group and 91 were assigned to the FeSO4 group. There were a total of 40 subjects that were not included in the ITT population (21 in the Venofer arm group and 19 in the FeSO4 group). A total of 16 patients had unstable EPO doses within the 8 weeks prior to randomization and 5 patients had no post-baseline data in the 2 treatment arms. Therefore, the ITT population for Venofer group includes 79 patients while the ITT population for the FeSO4 group includes 82 patients. Of the 2 patients who were discontinued from the study in the oral iron group listed as "other", 1 used an inhaler for asthma and 1 did not have an elevated serum creatinine, a decreased CrCL or an anemia due to renal insufficiency. Eight patients in the Venofer group and 8 patients in the FeSO4 group did not complete

the study due to requirement of an intervention. Intervention was defined as follows:

- Increase in EPO dose for any reason.
- Blood transfusion.
- Use of iron outside of protocol.

Therefore, there were 70 patients in the Venofer group and 72 patients in the FeSO4 group who completed the study.

The tables below show the demographics and baseline characteristics of the safety population. Patients in the FeSO4 treated group were somewhat older than those in the Venofer treated group. More blacks and fewer whites were in the FeSO4 treated group compared to the Venofer treated group. The baseline CrCL actually ranged from $\geq$ 90ml/min/1.73m^2 to $\leq$ 15ml/min/1.73m^2. More patients in the FeSO4 treated group had a CrCL $\leq$ 30 ml/min than did patients in the Venofer treated group.

Table 6.2a Demographic Characteristics at Baseline (Safety Population)

Demographic Characteristic	Venofer® (N=91)	Oral Iron (N=91)
Age (years)		
Mean (SD)	61.6 (15.10)	64.0 (13.38)
Median	63	66
Minimum - Maximum	25 - 86	21 - 86
<65	49 (53.8%)	43 (47.3%)
≥65	42 (46.2%)	48 (52.7%)
Gender		
Male	29 (31.9%)	27 (29.7%)
Female	62 (68.1%)	64 (70.3%)
Race		
Black	31 (34.1%)	40 (44.0%)
Caucasian	55 (60.4%)	46 (50.5%)
Other	5 (5.5%)	5 (5.5%)
Asian	2 (40.0%)	1 (20.0%)
Hispanic	3 (60.0%)	4 (80.0%)
Weight (kg)	(N=91)	(N=89)
Mean (SD)	84.9 (22.59)	84.6 (23.57)
Median	84	84
Minimum - Maximum	46 - 144	44 - 151

SD=Standard Deviation
Cross-reference: Appendix Table 2.1.1 and Appendix Listing 4.1

Six subjects (3 Venofer® and 3 oral iron) had a prior history of iron intolerance (oral iron). Each of these subjects' primary symptom associated with oral iron administration included diarrhea, stomach cramps, stomach upset, and nausea (Appendix Table 2.4).

Table 6.2b Baseline Characteristics (Safety Population)

Baseline Characteristic	Venofer® (N=91)	Oral Iron (N=91)
Erythropoietin Status		
EPO User	41 (45.1%)	39 (42.9%)
Non-EPO User	50 (54.9%)	52 (57.1%)
Baseline Hemoglobin (g/dL)		
Mean (SD)	10.2 (0.65)	10.1 (0.71)
Median	10	10
Minimum - Maximum	8 - 11	8 - 11
Baseline TSAT (%)		
Mean (SD)	16.3 (5.30)	16.7 (5.02)
Median	17	17
Minimum - Maximum	3 - 25	4 - 25
<20%	58 (63.7%)	60 (65.9%)
Baseline Ferritin (ng/mL)		
Mean (SD)	91.0 (70.64)	100.6 (73.66)
Median	71	81
Minimum - Maximum	5 - 300	4 - 293
< 100 ng/mL	56 (61.5%)	53 (58.2%)
≥ 100 ng/mL	35 (38.5%)	38 (41.8%)
Baseline TSAT < 20% and Ferritin < 100 ng/mL	35 (38.5%)	39 (42.9%)
Baseline Creatinine Clearance (mL/min/1.73 m^2)		
Mean (SD)	29.5 (14.93)	29.2 (20.55)
Median	29	24
Minimum - Maximum	9 - 78	7 - 113
≤ 30 mL/min/1.73 m^2	52 (57.1%)	61 (67.0%)
> 30 mL/min/1.73 m^2	39 (42.9%)	30 (33.0%)
Prior Iron Intolerance		
Yes	3 (3.3%)	3 (3.3%)
Oral Iron	2 (2.2%)	2 (2.2%)
Other	1 (1.1%)	1 (1.1%)

SD=Standard Deviation
Cross-reference: Appendix Table 2.1.1 and Appendix Listing 4.2

There were 9 subjects in the Venofer group and 6 subjects in the oral iron group who had protocol violations due to inclusion/exclusion criteria. Six of the subjects were granted exceptions by the sponsor to participate in the study. The most common violation was the exclusion criteria of a known sensitivity to a component of Venofer or FeSO4.

Drugs

Venofer was administered as 1000 mg in divided IV doses over a 14 day period. Two regimens were used. Some patients received 200 mg IV (40 mg/min injected over 2-5 minutes) on 5 different occasions within a 14 day period. The remainder received 500mg as a 2mg/minute infusion over 3.5 to 4 hours on days 0 and 14. For subjects who weighed < 70 kg, the 500mg was given over 5 hours after several patients suffered hypotensive events. FeSO4 was given orally as 325 mg (65mg elemental Fe) tablets tid on days 1 through 56. The duration of treatment was 8 weeks.

The dosing for the FeSO4 group was chosen based on standard recommendations for the treatment of FeDA. The dose for the Venofer group was based on the 38 previously published studies using higher doses, ranging from 200mg to 700-800 mg involving more than 2000 patients. No life threatening reactions were observed in these studies when Venofer was administered at doses as high as 700-800 mg.

The table below shows the degree of compliance during the study as well as the normalized compliance (defined as the **subject's compliance calculated over the** actual time in the study compared to the expected time).

Table 6.3a Summary of Treatment Compliance During the Study (Intent-to-Treat Population)

% Compliance	Venofer® (N=79)	Oral Iron (N=82)
Mean (SD)	97.3 (13.75)	82.7 (24.73)
95% Confidence Interval of Mean	94.3, 100.4	77.3, 88.1
Median	100.0	94.3
Minimum - Maximum	20.0 - 100.0	2.4 – 108.3
Subjects ≥80% Compliant	76 (96.2%)	55 (67.1%)
Subjects ≥80% Compliant (Normalized)	76 (96.2%)	63 (76.8%)

Cross-reference: Appendix Tables 5.2B and 5.3.2 and Appendix Listing 8

The table below shows the degree of exposure to Fe between the two treatment groups in the study.

Table 6.6a Summary of Extent of Exposure (Safety Population)

Total Dose of Iron (mg) Received	Venofer® (N=91)	Oral Iron (N=91)
Mean (SD)	932.7 (211.21)	9115.0 (2656.21)
95% Confidence Interval of Mean	889.4, 976.1	8569.2, 9660.8
Median	1000.0	10335.0
Minimum – Maximum	80.0 - 1000.0	260.0 - 13000.0

SD=Standard Deviation
Cross-reference: Appendix Table 5.1A and Appendix Listing 8

Efficacy Endpoints

The primary efficacy endpoint was the proportion of subjects in the ITT population in each treatment arm who had an increase in Hgb of at least 1.0 g/dl at any time between baseline and the end of the study or time of intervention. Secondary efficacy endpoints for the ITT population were as follows:

- Clinical response rate between the 2 treatment groups in the combined non-EPO and EPO treated population defined as an increase in Hgb of at least 1.0 g/dl and an increase in ferritin of at least 160 ng/ml anytime between baseline and the end of the study or time of intervention. The changes in ferritin and Hgb did not have to be simultaneous.
- The proportion of subjects with an increase in Hgb of at least 1.0 g/dl between baseline and the end of the study or time of intervention in subjects with a baseline ferritin < 100 ng/ml.
- The proportion of subjects with an increase in hemoglobin of at least 1.0 g/dl between baseline and the end of the study or time of intervention in EPO versus non-EPO treated patients.
- Clinical response in subjects with a baseline ferritin < 100 ng/ml.
- Clinical response in subjects with a baseline ferritin ≥ 100 ng/ml.
- Maximum change in Hgb over baseline.
- Maximum change in ferritin over baseline.
- Time to maximum Hgb defined as the days between the first dose of study drug administered and the day when the maximum on-study Hgb was reached.
- Time to maximum ferritin defined as the days between the first dose of the study drug administration and the day when the maximum on-study ferritin was reached.
- Time to response defined as the days between the study drug administration and the day of the first evidence of clinical response
- Time to intervention defined as the days between the study drug administration and the day of intervention or end of study whichever came first. The observation was censored if no intervention was necessary.
- Change in Hgb, ferritin and TSAT from baseline to day 42 and day 56.
- Comparison in changes from baseline in various combinations to support clinical response.

The primary efficacy analysis compared the proportion of subjects with an increase in Hgb of at least 1.0 g/dl at any time between baseline and the end of the study or time of intervention. A greater proportion of Venofer treated subjects (44.3%, 35/79) compared to FeSO4 treated subjects (28%, 23/82) had an increase in Hgb ≥ 1.0 g/dl during this study (p=0.034) as is shown in the table below.

Table 6.4a Summary of the Proportion of Subjects With ≥ 1.0 g/dL Increase From Baseline in Hemoglobin During the Study (Intent-to-Treat Population)

	Number (%) Subjects		
	Venofer® (N=79)	Oral Iron (N=82)	Fisher's Exact p-value
Anytime During Study	35 (44.3%)	23 (28.0%)	0.0344

Cross-reference: Appendix Table 3.1.1.1 and Appendix Listing 7

The table below shows the summary of the proportion of subjects with ≥ 1.0 g/dl increase from baseline in hemoglobin by each visit during the study. A greater proportion of Venofer treated patients compared to FeSO4 treated patients had a ≥ 1.0 g/dl increase from baseline in Hgb at each visit. The differences between the groups in terms of Hgb response was most pronounced at day 42 and day 56.

Table 6.4b Summary of the Proportion of Subjects With ≥ 1.0 g/dL Increase From Baseline in Hemoglobin By Each Visit During the Study (Intent-to-Treat Population)

	n/N (%) Subjects		
Scheduled Visit	Venofer® (N=79)	Oral Iron (N=82)	Fisher's Exact p-value
By Day 14	11 (13.9%)	6 (7.3%)	0.2054
By Day 28	22 (27.8%)	12 (14.6%)	0.0530
By Day 42	30 (38.0%)	18 (22.0%)	0.0381
By Day 56/End-of-Study	35 (44.3%)	23 (28.0%)	0.0344

n = subjects who attained at least 1.0 g/dL increase from baseline in hemoglobin at each Day.
N = total number of subjects at each Day.
Cross-reference: Appendix Table 3.1.2.1 and Appendix Listing 7

Both Venofer and FeSO4 were able to increase the mean Hgb concentration (in g/dl) from baseline at day 42 and day 56. However, the Venofer treated patients had a greater mean increase in Hgb from baseline to days 42 and 56 compared to FeSO4 treated patients as is shown in the table below. Similar trends were observed for ferritin and TSAT levels at days 42 and 56. There was no difference between the treatment groups in those patients that were profoundly Fe deficient (i.e. ferritin < 100ng/ml) in the number of subjects who had a ≥ 1.0g/dl increase in Hgb from baseline (21/49 patients (42.9%) in the Venofer group compared to 16/46 patients (34.8%) in the FeSO4 group (p=0.4199)).

Summary of Mean Changes from Baseline to the Day 42 and Day 56 visits in Hgb (g/dl) and Ferritin (ng/ml) and TSAT (%) During the Study (ITT population)*

	Venofer (N=79)				FeSO4 (N=82)				Difference p-value
	N	Baseline (BL) Standard Deviation (SD)	Change from BL (SD)	p value	N	BL (SD)	Change from BL (SD)	p value	
Hgb Day 42	64	10.3 (0.59)	0.7 (0.91)	<0.0001	65	10.1 (0.69)	0.4 (0.82)	0.0007	0.0298
Hgb Day 56	72	10.3 (0.61)	0.7 (0.94)	<0.0001	71	10.1 (0.70)	0.3 (0.90)	0.0028	0.0267

*Adapted from sponsor's table 6.4g

Comparisons of changes from baseline in various combinations of laboratory parameters are shown in the table below. Generally, there were statistically significant differences between the treatment groups for all specified laboratory change criteria.

Table 6.4m Summary of the Proportion of Subjects Achieving Specified Laboratory Change Criteria at Day 42 and Day 56/End-of-Study (Intent-to-Treat Population)

Change Criteria[a]	Scheduled Visit	n/N (%) Subjects		Fisher's Exact p-value
		Venofer®	Oral Iron	
Ferritin	Day 42	62/65 (95.4%)	0/66 (0%)	< 0.0001
	Day 56/EOS	67/72 (93.1%)	2/72 (2.8%)	< 0.0001
TSAT	Day 42	61/64 (95.3%)	52/66 (78.8%)	0.0078
	Day 56/EOS	70/72 (97.2%)	61/72 (84.7%)	0.0169
Hemoglobin and TSAT	Day 42	24/63 (38.1%)	12/64 (18.8%)	0.0186
	Day 56/EOS	27/64 (42.2%)	18/62 (29.0%)	0.1399
Hemoglobin, Ferritin, and TSAT	Day 42	22/63 (34.9%)	0/64 (0%)	< 0.0001
	Day 56/EOS	28/72 (38.9%)	1/71 (1.4%)	< 0.0001
Ferritin and TSAT	Day 42	58/64 (90.6%)	0/66 (0%)	< 0.0001
	Day 56/EOS	65/72 (90.3%)	2/72 (2.8%)	< 0.0001

n = subjects who achieved criteria at each Day.
N = total number of subjects at each Day.
a Ferritin Change ≥ 160 ng/mL; TSAT Change ≥ 5%; Hemoglobin Change ≥ 1 g/dL
Cross-reference: Appendix Table 3.1.2.2 and Appendix Listing 7

The percent of patients with an increase in Hgb ≥ 1.0 g/dl was greater in the Venofer group than in the FeSO4 group in both the EPO users (17/32 patients, 53.1% compared to 10/31 patients, 32.2%, respectively) and non-EPO users

(18/47 patients, 38.3% compared to 13/51 patients, 25.5%, respectively). These differences were not statistically significantly different. When restricted to those subjects with baseline CrCL $\leq$ 45ml/min/1.73m^2, the treatment group differences in the percent of subjects achieving $\geq$ 1.0g/dl increase from baseline in Hgb were 30/67 patients (44.8%) in the Venofer group and 15/70 patients (21.4%) in the FeSO4 group (p=0.0036). When restricted to those subjects with a baseline CrCL $\leq$ 45ml/min/1.73m^2, the treatment group differences in the percent of subjects achieving $\geq$ 1.0g/dl increase from baseline in Hgb was 14/27 patients (51.9%) in the Venofer group compared to 9/30 patients (30.0%) in the FeSO4 group (p=0.0931) in EPO users and 16/40 patients (40.0%) in the Venofer group compared to 6/40 patients (15.0%) in the FeSO4 group (p=0.0123) in non-EPO users.

There was no difference between the treatment groups in patients < 65 years of age. In this subgroup, there was a $\geq$ 1.0g/dl increase from baseline in Hgb (15/41 patients (36.6%) in the Venofer group compared to 13/39 patients (33.3%) in the FeSO4 group (p=0.7605)). However, there was a greater proportion of patients > 65 years of age that had a $\geq$ 1.0g/dl increase from baseline in Hgb (20/38 patients (52.6%) in the Venofer group compared to 10/43 patients (23.3%) in the FeSO4 group (p=0.0063)). In addition, the proportion of subjects achieving a $\geq$ 1.0g/dl increase in Hgb from baseline was greater in the Venofer group compared to the oral iron group in both Blacks and Caucasians. There were also no differences observed between the treatment groups in the mean change from baseline to day 56 in the measurement of quality of life.

Ethical Considerations

The study was performed in accordance with the U. S. Code of Federal Regulations on the Protection of Human Subjects, Institutional Review Board (IRB), the 2000 Edinburgh Scotland Revision of the Declaration of Helsinki, all local and state regulations, 21 CFR§312 and applicable International Conference on Harmonization guidelines. Each site had the protocol and the informed consent approved by an appropriate IRB. The investigator obtained informed consent and a copy was provided to the subject. Translations of the informed consent were certified by a qualified translator and their use was documented.

Safety Assessment

The safety variables included adverse events, serious adverse events and laboratory evaluations including hematology, iron indices, chemistry and C-reactive protein. A pregnancy test was performed at the enrollment visit for all females.

All safety analyses were performed using the safety population defined as all subjects who received at least one dose of study drug. The overall incidence of treatment emergent adverse events was similar between the Venofer group and

the FeSO4 group (70.3% compared to 64.8% respectively). The most commonly experienced treatment emergent adverse events (≥ 5%) in the Venofer group were dysgeusia (7.7%), peripheral edema (7.7%), constipation (5.5%), diarrhea (5.5%), dizziness (5.5%), hypertension (5.5%) and nausea (5.5%). The most commonly experienced treatment emergent adverse events in the FeSO4 group were constipation (12.1%), diarrhea (9.9%), nausea (9.9%), edema (8.8%), fatigue (6.6%), vomiting (6.6%), urinary tract infection (6.6%) and fecal occult blood positivity (5.5%). The majority of the treatment emergent adverse events experienced during the study were considered to be grade 1 or 2 in intensity. During the study, at least one drug related treatment emergent adverse event was experienced by 23.1% (21/91) of the subjects in the Venofer group and 18.7% (17/91) of the subjects in the FeS04 group. The largest difference between the groups in drug-related treatment emergent adverse events was for the incidence of gastrointestinal disorders (8.8% in the Venofer group and 17.6% in the FeSO4 group). The Venofer group had a higher incidence of dysgeusia (5.5%), characterized as an abnormal taste sensation, compared to the FeSO4 group (0%). The oral iron group had a higher incidence of constipation (8.8%), diarrhea (3.3%) and nausea (3.3%) compared to the Venofer group (1.1%, 0% and 1.1% respectively). There were no clinically important trends observed when treatment emergent adverse events were stratified according to age, gender, race or dose.

No deaths were reported during this study. Serious adverse events were experienced by 11.0% (10) of subjects in the Venofer compared to 6.6% (6) of subjects in the FeSO4 group. Premature discontinuation from the study due to adverse events occurred in 3.3% (3) subjects in the Venofer group compared to 2.2% (2) subjects in the FeSO4 group. Adverse events leading to premature discontinuation in the 3 Venofer patients were all considered study drug related and included hypotension, dyspnea and nausea. Adverse events leading to premature discontinuation in the 2 patients in the FeSO4 group were hip fractures. Grade 3 hypotension was experienced by 2 patients in the Venofer group within approximately 30 minutes of Venofer administration at the 500 mg dose and was considered to be probably related to the study drug as the patients appeared to initially have hypersensitivity type reactions with local swelling of the hand and wrist followed by the hypotensive episodes. Both subjects weighed <70 kg (62.5 kg and 46.2 kg). Both subjects prematurely discontinued the study drug due to these events. The hypotension in both patients resolved without treatment intervention. A third patient in the Venofer group (200mg) with a history of chronic obstructive pulmonary disease experienced grade 4 hypotension and respiratory failure on day 36 (21 days after completing Venofer administration) which appeared to be related to septic shock.

Evaluation of the vital signs and physical examinations showed no clinically important trends associated with Venofer or FeSO4 administration. There were no clinically meaningful differences between the groups in the analysis of hematology and biochemistry variables.

The table below shows the number and types of treatment emergent adverse events.

Table 6.6b Treatment-Emergent Adverse Events Experienced by 3 or More Subjects in Either Treatment Group (Safety Evaluable Population)

MedDRA SOC Preferred Term	Venofer® (N=91)	Oral Iron (N=91)
At Least One Treatment-Emergent Adverse Event	**64 (70.3%)**	**59 (64.8%)**
Ear and Labyrinth Disorders	3 (3.3%)	2 (2.2%)
Ear Pain	3 (3.3%)	0
Gastrointestinal Disorders	24 (26.4%)	31 (34.1%)
Constipation	5 (5.5%)	11 (12.1%)
Diarrhea NOS	5 (5.5%)	9 (9.9%)
Dysgeusia	7 (7.7%)	0
Nausea	5 (5.5%)	9 (9.9%)
Vomiting NOS	3 (3.3%)	6 (6.6%)
General Disorders and Administration Site Conditions	22 (24.2%)	17 (18.7%)
Fatigue	3 (3.3%)	6 (6.6%)
Injection Site Extravasation	3 (3.3%)	0
Injection Site Pain	3 (3.3%)	0
Edema NOS	4 (4.4%)	8 (8.8%)
Peripheral edema	7 (7.7%)	2 (2.2%)
Infections and Infestations	8 (8.8%)	12 (13.2%)
Urinary Tract Infection NOS	1 (1.1%)	6 (6.6%)
Investigations	8 (8.8%)	9 (9.9%)
Fecal Occult Blood Positive	2 (2.2%)	5 (5.5%)
Metabolism and Nutrition Disorders	9 (9.9%)	3 (3.3%)
Gout	4 (4.4%)	1 (1.1%)
Musculoskeletal and Connective Tissue Disorders	19 (20.9%)	6 (6.6%)
Back Pain	2 (2.2%)	3 (3.3%)
Myalgia	4 (4.4%)	0
Pain in Extremity	4 (4.4%)	0
Nervous System Disorders	10 (11.0%)	5 (5.5%)
Dizziness	5 (5.5%)	1 (1.1%)
Respiratory, Thoracic, and Mediastinal Disorders	14 (15.4%)	3 (3.3%)
Cough	3 (3.3%)	1 (1.1%)
Dyspnea	4 (4.4%)	0
Vascular Disorders	8 (8.8%)	2 (2.2%)
Hypertension NOS	5 (5.5%)	2 (2.2%)
Hypotension NOS	3 (3.3%)	0

NOS=not otherwise specified.
Cross-reference: Appendix Table 6.3.1 and Appendix Listing 9.1

During the study, at least 1 drug-related treatment-emergent adverse event was experienced by 23.1% (21/91) of the subjects in the Venofer® group and 18.7% (17/91) of the subjects in the oral iron group (Appendix Table 6.1). The most commonly experienced drug-related treatment-emergent adverse events in the Venofer® group was dysgeusia (5.5%). The most commonly experienced drug-related treatment-emergent adverse events in the oral iron group was constipation (8.8%). A summary of drug-related treatment-emergent adverse events experienced by 3 or more subjects in either treatment group during the study is presented in Table 6.6c.

The table below shows the number and types of serious adverse events.

Table 6.6d Subjects Who Experienced Serious Adverse Events (Safety Evaluable Population)

Subject Number	Age/Sex/ Race/Dose[a]	Preferred Term	Relative Day[b]	Severity	Causality[c]	Treatment
Venofer®						
918-109	60/M/B/ 200 mg	Fluid overload	3	Grade 4	None	Medication
902-828	50/F/C/ 500 mg	Flank pain	24	Grade 3	None	Medication
910-847	67/F/C/ 200 mg	Angina pectoris	5	Grade 3	None	Medication
908-422	67/F/C/ 500 mg	Hypotension NOS[d]	1	Grade 3	Probable	Medication
		Dyspnea[d]	1	Grade 3	Probable	Medication
904-411	49/F/C/ 200 mg	Pleural effusion	45	Grade 3	None	Surgical
919-003	71/M/C/ 200 mg	Intraoperative hemorrhage	34	Grade 3	None	Medication
928-425	77/F/C/ 200 mg	Hyponatremia	26	Grade 1	None	None
901-551	59/F/C/ 200 mg	Mental status changes	36	Grade 4	None	Medication
		Hypotension NOS	36	Grade 4	None	Medication
		Respiratory failure	36	Grade 4	None	Medication
		Sepsis NOS	36	Grade 4	None	Medication
902-307	45/M/C/ 200 mg	Lobar pneumonia NOS	16	Grade 3	None	Medication
910-606	71/M/B/ 200 mg	Renal failure acute	43	Grade 3	None	Other
Oral Iron						
916-864	43/F/B	Fluid overload	24	Grade 2	None	Other
905-402	77/F/C	Hip fracture[d]	26	Grade 4	None	Surgical
910-403	67/F/C	Hip fracture[d]	45	Grade 3	None	Surgical
901-302	74/M/B	Syncope	14	Grade 3	None	Medication
901-756	60/M/C	Pneumonia NOS	33	Grade 3	None	Medication
902-889	59/F/B	Fracture reduction	30	Grade 4	None	Surgical

F=female; M=male; B=Black; C=Caucasian; NOS=not otherwise specified
a Dose is presented for the Venofer® group.
b Relative day = onset date – study drug date.
c As assessed by the Investigator.
d Event led to premature discontinuation.
Cross-reference: Appendix Listing 9.5

In the safety population there was a mean decrease in platelet count of 20.5 $x10^9$/l (standard deviation 41.1$x10^9$/l) from a mean baseline platelet count of 247.3 $x10^9$/l (standard deviation 84.3 $x10^9$/l) in the Venofer group compared to a mean decrease in platelet count of 7.6 $x10^9$/l (standard deviation 49.71 $x10^9$/l) from a mean baseline platelet count of 245.8 $x10^9$/l (standard deviation 90.23 $x10^9$/l) in the FeSO4 group.

Statistical Methods

The analysis of the primary endpoint was the unstratified comparison of the Hgb response rate between the two study groups in the combined non-EPO and EPO treated population using a 2-sided Fisher's exact test at the 0.05 significance level.

In addition, 2 summaries were provided for the day 56 visit. One was based on the observed case method while the other was based on the last observation carried forward method, in which subjects who discontinued from the study prior to day 56 were evaluated based on their last non-missing post-baseline value.

Treatment effect was evaluated using the Cochran-Mantle-Haenszel test controlling for center. A logistic regression model was used to evaluate the effect of potential covariates on the odds of achieving the 1.0 g/dl Hgb response at the day 56 visit based on the last observation carried forward method.

An analysis of covariance (ANCOVA) model was used to assess treatment effect on the quality of life including effects of treatment, baseline score, center, treatment-by-center interaction and treatment-by-baseline score.

No formal statistics were provided for adverse event summary tables.

Conclusions

The data from trial 1VEN03027 show that a statistically significantly greater proportion (p=.0344) of Venofer treated subjects (35/79, 44.3%) had an increase in Hgb ≥ 1.0g/dl compared to those treated with oral FeSO4 (23/82, 28.0%). A greater proportion of Venofer treated patients (67/72, 93.1%) had an increase in serum ferritin to ≥160ng/ml during the study compared to FeSO4 treated patients (2/72, 2.8%). The mean change in Hgb from baseline to day 42 and day 56 (end of study) showed statistically significant differences in Hgb between the 2 groups but the absolute differences in Hgb were clinically unimportant (0.4 and 0.3 g/dl, respectively). Mean increases in Hgb were greater for Venofer treated patients compared to FeSO4 treated patients whether or not concomitant EPO was administered. The design of 1VEN03027, which required stable EPO dosing for 8 weeks prior to randomization, allowed for comparison of the response due to Venofer and FeSO4 while minimizing the confounding effect of exogenous EPO. However, this is the only adequate and well controlled study the sponsor has performed to support the use of Venofer in non-HD CKD patients.

Ferritin and TSAT levels increased significantly from baseline after treatment with Venofer, but only marginally after oral FeSO4 administration. The 2000 K/DOQI recommendations state that CKD patients should have sufficient iron to achieve and maintain an Hgb/Hct of 11 to 12 g/dL/33% to 36%. The recommendations further state that in order to achieve and maintain this target Hgb/Hct, sufficient iron should be administered to maintain a TSAT of ≥20% and a serum ferritin level of ≥100 ng/ml. The evidence to support these target TSAT and ferritin levels is not strong at present. Therefore, the clinically most meaningful marker for successful Fe therapy in FeDA in CKD is an improvement in Hgb.

The incidence of treatment emergent adverse events between the treatment groups was similar (70.3% for the Venofer group compared to 64.8% in the FeSO4 group). Venofer was associated with 2 serious adverse events of hypotension possibly related to hypersensitivity which caused the premature discontinuation of the study drug.

The cause of the slight decrease in platelet count in patients given Venofer is unclear and is probably not clinically meaningful. It is possible that the mechanism represents an interaction between EPO, iron repletion and megakaryocytopoiesis, as has been reported in studies in iron deficient rats treated with both EPO and intravenous iron.[2]

Based on these results, the sponsor's proposed expanded indication for Venofer (i.e. treatment of FeDA in non-HD dependent CKD patients receiving and not receiving EPO replacement therapy) should be approved.

[2] Loo, M and Beguin, Y. The effects of recombinant human erythropoietin on platelet counts is strongly modulated by the adequacy of iron supply. Blood. 1999; 93(10):3286-3293.

III. Recommendations

The following information should be forwarded to the sponsor:

The expanded indication for Venofer for the treatment of iron deficiency anemia in non-dialysis dependent chronic kidney disease patients receiving or not receiving erythropoietin replacement therapy should be approved.

The approval is contingent upon an agreement to changes made in the label submitted by the sponsor.

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/s/

Andrew Dmytrijuk
6/10/05 12:09:31 PM
MEDICAL OFFICER

George Shashaty
6/15/05 08:44:19 AM
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Clinical Review
NDA 21-135/SE1-008

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Sponsor:	Luitpold Pharmaceuticals, Inc.
Drug name:	Venofer (Iron Sucrose Injection)
Drug class:	Intravenous iron product
Indication:	Treatment of iron deficiency anemia in chronic kidney disease (CKD) patients on erythropoietin
Date submitted:	August 15, 2003; February 20, 2004; February 26, 2004
Review completed:	May 17, 2004
Medical Reviewer:	Min Lu, M.D., M.P.H.

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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CKD	Chronic Kidney Disease
CI	Confidence Interval
CMH	Cochran-Mantel-Hanszel
CrCl	Creatinine Clerance
CRF	Case report form
DL	Deciliter
ECG	Electrocardiogram
EPO	Erythropoietin
ESRD	End Stage Renal Disease
Fe[III]	Ferric Iron
G	Gram
GTP	Gamma-glutamyl transpeptidase
Hb	Hemoglobin
Hct	Hematocrit
HIV	Human immunodeficiency virus
IRB	Institutional Review Board
ITT	Intent-To-Treat
IV	Intravenous
L	Liter
LDH	Lactic dehydrogenase
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
Mg	Milligram
ml	Milliliter
NaCl	Sodium chloride
Ng	Nanogram
NKF-DOQI	National Kidney Foundation-Dialysis Quality Initiative
NOS	Not Otherwise Specified
PD	Peritoneal Dialysis
PP	Per Protocol
QOL	Quality of Life
r-HuEPO	Recombinant human erythropoietin
RBC	Red blood cell
SAE	Serious adverse event
SD	Standard Deviation
SEM	Standard error *of* the mean
SLE	Systemic lupus erythematosis
SOB	Shortness of Breath
TIBC	Total iron binding capacity
TID	Three times daily
TSAT	Transferrin saturation
WBC	White Blood Cell

Clinical Review for NDA 21-135/SE1-008

Executive Summary

I. Recommendations

A. Recommendation on Approvability

From a clinical perspective, this reviewer recommends Venofer is not approvable for the proposed indication expansion from "treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy" to "treatment of iron deficiency anemia in chronic kidney disease (CKD) patients on erythropoietin".

The clinical deficiencies include the following:

1. Only one study was conducted in patients with chronic kidney disease not on dialysis. The study failed to demonstrate that Venofer is superior to oral iron in an increase in hemoglobin at Day 43 from baseline as planned in the study protocol. The primary efficacy results showed that the difference in mean change in hemoglobin from baseline between Venofer and oral iron groups was not statistically significant (1.0 g/dL vs. 0.7 g/dL, p=0.14).
2. Initiation of epoetin therapy in the majority of study patients (83% in the Venofer group and 90% in the oral iron group) in the study may have contributed significantly to an increase in hemoglobin at Day 43 from baseline in both treatment groups.
3. A significant proportion of randomized patients were not included in the primary efficacy analysis in the study [26 % (14/53) in the Venofer group and 12% (6/49) in the oral iron group)].
4. In the study patients in the Venofer treatment group experienced more adverse events (except for gastrointestinal disorders), serious adverse events, and premature discontinuation due to adverse events than did patients in the oral treatment group.
5. Safety information in chronic kidney disease patients not on dialysis is limited.

To resolve the clinical deficiencies, the sponsor should conduct an adequate and well-controlled study to support the efficacy and safety of Venofer for the treatment of iron deficiency in chronic kidney disease patients not on dialysis. The study should be a randomized, parallel groups controlled study. The study patients should be patients who have received epoetin therapy with a stable dose for at least 3 months before the study and who will maintain the previous epoetin dose as much as possible during the study.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

There is no recommendation on phase 4 study or risk management based on the current submission.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Product name: Venofer

Drug class: Intravenous iron products

One trial (1VEN90912) was conducted in 102 patients with chronic kidney disease not on dialysis to support the proposed expansion of the indication from "treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy" to "treatment of iron deficiency anemia in chronic kidney disease (CKD) patients on erythropoietin".

A total of 96 patients with chronic kidney disease not on dialysis were exposed to at least one dose of Venofer 200 mg in the trial.

B. Efficacy

One study (1VEN99012) was submitted to support the indication for treatment of iron deficiency anemia in chronic kidney disease patients not on dialysis.

Study 1VEN 99012 was a multicenter, randomized, open-label, parallel groups study of Venofer 200 mg IV weekly for 5 doses as compared to oral iron (ferrous sulfate) 325 mg three times a day for 29 days in patients with chronic kidney disease not on dialysis. Patients with creatinine clearance < 40 ml/min, hemoglobin < 10.5 g/dL, TSAT < 25% and serum ferritin < 300 ng/mL were enrolled in the study. The primary efficacy endpoints of the study were the mean changes at Day 43 from baseline in hemoglobin and ferritin levels. The differences in the mean change in hemoglobin and ferritin from baseline between the two treatment groups were tested (each was to be tested at α=0.025).

A total of 102 patients (53 patients in the Venofer group and 49 patients in the oral iron group) were randomized, 96 patients (48 patients in each group) were treated, and 82 patients (39 patients in the Venofer group and 43 patients in the oral iron group) were evaluated for primary efficacy endpoints in the study. Patients ranged in age from 27 to 91 years (mean ages of 62 years in the Venofer group and 60 year in the oral iron group) with more than 60% of females (60% in the Venofer group and 71% in the oral iron group). Patients were Caucasian (38% in the Venofer group and 44% in the oral iron group), Hispanic (35% in the Venofer group and 23% in the oral iron group), Black (23% in the Venofer group and 29% in the oral iron group), and Asian (4% in each group). The majority of patients were epoetin naïve (83% in the Venofer group and 90% in the oral iron group).

The study failed to demonstrate that Venofer is superior to oral iron in increasing hemoglobin at Day 43 from baseline in patients with chronic kidney disease not on dialysis (1.0 mg/dL in the Venofer group and 0.7 mg/dL in the oral iron group, p=0.14). The study showed a significant difference in an increase in ferritin level at Day 43 from baseline between the Venofer group and the oral iron group (288 ng/mL and -5.1 ng/mL, respectively, p<0.0001). However, change in hemoglobin is a more clinically relevant and important endpoint than change in ferritin for treatment of anemia in patients with chronic kidney disease not on dialysis since the main cause of anemia may not be iron deficiency in these patients.

The study showed significant increases in hemoglobin at Day 43 as compared to baseline in both treatment groups (p<0.02 in the Venofer group and p<0.002 in the oral iron group). Since the majority of patients were epoetin naïve and initiated epoetin treatment at the same time iron therapy was initiated in the study, an increase in hemoglobin from baseline may be due (at least in part) to new use of epoetin therapy in the both treatment groups. This was supported by an increase of hemoglobin (0.7 mg/dL) without an increase of ferritin level (-5.1 ng/mL) in the oral iron group. In a subgroup analysis, in patients with ferritin <100 ng/mL at baseline (20 in the Venofer group and 29 in the oral iron group) there was greater increase in hemoglobin from baseline in the Venofer group as compared to the oral iron group (1.4 g/dL and 0.9 g/dL, respectively, p=0.046).

The secondary efficacy analyses had similar findings. The results showed no significant difference in an increase in hematocrit at Day 43 from baseline between the Venofer group and the oral iron group (3.7% and 2.8%, respectively, p=0.12). There was a significant difference in an increase in TSAT at Day 43 from baseline between the Venofer group and the oral iron group (4.5% and 0.5%, respectively, p<0.0001).

It is noteworthy that a significant proportion of randomized patients were not included in the primary efficacy analysis [26 % (14/53) in the Venofer group and 12% (6/49) in the oral iron group)]. There were 9% of patients who discontinued study before the treatment and 17% of patients who did not complete the treatment in the Venofer group as compared to 2% and 10%, respectively, in the oral iron group. These may affect the efficacy and safety results of the study.

There was a notable imbalance in the iron status at baseline between the two treatment groups. Patients with TSAT <20% and ferritin <100 ng/mL were 33% in the Venofer group and 54% in the oral iron group. Also, there was an uneven distribution in age, gender and race between the two treatment groups.

Overall, the results from Study 1VEN99012 do not provide adequate support for the proposed indication for the treatment of iron deficiency anemia in patients with chronic kidney disease not on dialysis. An adequate and well-controlled study to demonstrate the effectiveness of Venofer in terms of an increase in hemoglobin in iron deficiency patients with chronic kidney disease not on dialysis will be needed. The study should be a randomized, parallel groups, controlled study. The study patients should be patients who have received epoetin therapy with a stable dose for at

least 3 months before the study and who will maintain the previous epoetin dose as much as possible during the study.

C. Safety

Only one study (Study 1VEN99012) was conducted in CKD patients not on dialysis by the sponsor. In this study, 48 patients were exposed to Venofer 200 mg by slow injection over 5 minutes for about 5 doses during the treatment phase and 78 patients were exposed to Venofer 200 mg for about 5 doses during the extended phase of the study. A total of 91 patients with CKD not on dialysis were exposed to Venofer 200 mg doses administered over 5 minutes in the study.

The overall incidences of treatment-emergent adverse events were similar between the Venofer group (87.5%, 42/48) and the oral iron group (89.6%,43/48) during the treatment phase. However, patients in the Venofer group experienced more cardiovascular, endocrine, general and administration site, nervous system, and vascular disorders than in the oral iron group while patients in the oral iron group experienced more gastrointestinal (except for taste disturbance and diarrhea) and skin and subcutaneous tissue disorders than in the Venofer group. Gastrointestinal disorders were the most commonly experienced treatment-emergent adverse events in both treatment groups (47.9% in the oral iron group and 35.4% in the Venofer group). AEs that occurred more frequently with Venofer treatment than with oral iron treatment included edema (8.3% vs. 2.1%), hyperglycemia (8.3% vs. 0%), taste disturbance (8.3% vs. 0%), dizziness (8.3% vs. 2.1%), hypertension aggravated (8.3% vs. 2.1%), and injection site burning (6.3% vs. 0%). AEs occurred more frequently with oral iron treatment than with Venofer treatment included nausea (16.7% vs. 12.5%) vomiting (12.5% vs. 8.3%), constipation (14.6% vs. 2.1%), pruritus (12.5% vs. 2.1%), abdominal pain (6.3% vs. 2.1%), weakness (6.3% vs. 0%), and nasal congestion (6.3% vs. 2.1%).

During the Extended Follow-Up Phase, at least one treatment-emergent adverse event was experienced by 78.2% (61/78) of the patients. The most commonly experienced treatment-emergent adverse events were diarrhea (12.8%), vomiting (9.0%), edema lower limb (9.0%), and arthralgia (9.0%).

During the whole study period, patients experienced more adverse events including cardiovascular disorders, diarrhea, taste disturbance, muscular pain, headache, dizziness, and hypertension with Venofer treatment than with oral iron treatment. Patients experienced more nausea and vomiting with oral iron treatment than with Venofer treatment.

More gastrointestinal disorders including constipation, nausea, and abdominal pain were attributed to oral iron treatment by the investigators. Taste disturbance, injection site reactions, limb pain, headache, dizziness, and pruritis were attributed to Venofer treatment by the investigators.

One patient died at 5 days after the last Venofer dose during the Extended Follow-Up Phase. The patient was a 74-year-old male with significant cardiac history who received Venofer 200 mg

during the Treatment Phase and 2 additional Venofer doses in the extended follow-up. The patient experienced 2 non-serious adverse events during the Treatment Phase (+2 edema on Day 8 and stiff neck on Day 35) that were considered by the Investigator to be not related to study medication. The cause of death was attributed to cardiopulmonary arrest secondary to coronary artery disease and hypertension and was considered unrelated to Venofer by the investigator. None of patients in the oral iron group died during the study and within 30 days after receiving study drug.

During the Treatment Phase, 7 (14.6%) patients in the Venofer group and 2 (4.2%) patients in the oral iron group experienced at least 1 serious adverse event. More patients experienced more SAEs including congestive heart failure, pulmonary edema, fluid overload, hyperglycemia, renal failure, and benign intracranial hypertension with Venofer treatment than with oral iron treatment. None of these serious adverse events was considered by the investigator to be related to study medication.

More patients discontinued the treatment prematurely due to AEs in the Venofer group (12.5%) than in the oral iron group (2.1%) during the treatment phase. An additional 10% of patients who were enrolled in the extended treatment phase prematurely discontinued the treatment due to adverse events.

No cases of hypersensitivity/allergic reaction were reported with Venofer treatment in the study. One case of hypotension was reported with oral iron treatment. No case of hypotension was reported during the treatment phase and 4 (5%) cases of hypotension were reported during the Extended Follow-Up Phase. None of these events was considered related to study drug by the investigators.

Only 3 published papers on studies in patients with CKD not on dialysis were found in a search of the literature. Safety information from these studies was limited.

Most adverse events reported by post-marketing spontaneous reports have been included in the current labeling.

In conclusion, there is limited safety information for Venofer in CKD patients not on dialysis. Clinical study 1VEN99012 showed that patients experienced more adverse events (except for gastrointestinal disorders), serious adverse events, and premature discontinuation due to adverse events with Venofer treatment than with oral iron treatment.

D. Dosing

The current recommended dosing regimen of Venofer is 100mg iron (5mL) by slow IV injection over 5 minutes or IV infusion as diluted solution over at least 15 minutes for treatment of iron deficiency anemia in patients undergoing chronic hemodialysis on erythropoietin.

The proposed new dosing regimen for treatment of chronic kidney disease not on dialysis is

[redacted])sed rate of

administration of Venofer 200 mg dose is _ Rapid administration and larger dose administration of intravenous iron products have been associated with more AEs (Bastabni B. et al, Nephrology 2003 Vol. 8: 8-10; Parkkinen J. et al, Nephrol Dial Transplant 2000, Vol. 15:1827-34; Zanen AL et al, Neprol Dial Transplant 1996, Vol. 11:820-4). The manufacturer of Venofer, Vifor (International) Inc. has recommended that the rate of administration of Venofer should not be more than 20 mg /min.

For efficacy, Study 1VEN90912 failed to demonstrated that Venofer 200 mg IV is superior to oral iron in increase in hemoglobin at Day 43 from baseline (1.0 g/dL vs. 0.7 g/dL, p=0.14).

For safety, patients experienced more adverse events (except for gastrointestinal disorders), serious adverse events, and premature discontinuation due to adverse events with Venofer treatment than with oral iron treatment.

To support the proposed higher dose with more rapid administration of Venofer for a new population, more safety data (about a total of 200 patients) should be collected to support the safety for Venofer with the new dose regimen in CKD patients not on dialysis possibly in a new trial designed to demonstrate the effectiveness of Venofer in this population.

In conclusion, the proposed new dose regimen is not adequately supported by the submitted efficacy and safety data. An additional adequate and well-controlled study will be needed to support the proposed new dose regimen.

E. Special Populations

Gender

There were 19 males and 29 females who received Venofer 200 mg dose in Study 1VEN90912 in the Treatment Phase. The mean increase in hemoglobin at Day 43 in the Venofer group was 0.8 g/dL in men (17 were available) and 1.2 g/dL in women (22 were available) as compared to the oral iron group (1.0 g/dL and 0.6 g/dl, respectively). It seems that women responded to Venofer better in increase in hemoglobin level than men based on a limited number of patients available. The mean increase in ferritin at Day 43 was 299 ng/mL in men (17 were available) and 280 ng/mL in women (22 were available) as compared to the oral iron group (-4.4 ng/mL and -5.4 ng/mL, respectively). There was no difference in increase in ferritin level between men and women.

The gender effect on safety of Venofer 200 mg was not analyzed by the sponsor.

Age

There were 22 patients with age <65 years and 26 patients with age ≥65 years who received Venofer 200 mg dose in Study 1VEN90912. The mean increase in hemoglobin at Day 43 in the Venofer group was 0.8 g/dL in patients <65 years (17 were available) and 1.2 g/dL in patients ≥65 years (22 were available) as compared to the oral iron group (0.6 g/dL and 0.9 g/dl, respectively). The mean increase in ferritin at Day 43 was 261 ng/mL in patients <65 years (17 were available) and 309 ng/mL in patients ≥65 years (22 were available) as compared to the oral

iron group (0.4 ng/mL and -14 ng/mL, respectively). This suggests that patients with age ≥65 years responded to Venofer better in increase in hemoglobin and ferritin levels than those with age <65 years, based on the limited number of patients available.

The age effect on safety of Venofer 200 mg was not analyzed by the sponsor.

Race

There were 18 Caucasian, 11 Black and 19 other races (17 Hispanic and 2 Asian) patients who received Venofer 200 mg dose in the Treatment Phase in Study 1VEN90912. The mean increase in hemoglobin at Day 43 in the Venofer group was 0.7 g/dL in Caucasian (15 were available), 0.4 in Black (6 were available), and 1.5 g/dL in other races (18 were available) patients as compared to the oral iron group (1.0 g/dL, 0.1 g/dL and 0.9 g/dl, respectively). The mean increase in ferritin at Day 43 in the Venofer group was 305 ng/mL in Caucasian (15 were available), 237 ng/mL in Black (6 were available), and 290 ng/mL in other races (18 were available) patients as compared to the oral iron group (-15 ng/mL, 1.9 ng/mL, and 5.9 ng/mL, respectively). No conclusion on race effect can be made because of the limited number of patients available in the study.

The race effect on safety of Venofer 200 mg was not analyzed by the sponsor.

Renal impairment

All study patients had chronic kidney disease not on dialysis (creatinine clearance <40 mL/min).

Hepatic impairment

No study was performed in patients with hepatic impairment.

Pregnancy

No study was performed in pregnant subjects.

Pediatric patients

A pharmacokinetic study of Venofer in adolescents was completed and submitted to the Agency for review. An efficacy and safety study of Venofer in pediatric population (2 to 12 years) for treatment of iron deficiency anemia in patients undergoing chronic dialysis is ongoing. Both studies are Phase 4 commitments.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Drug established and proposed trade name: Venofer

Drug class: Intravenous iron products

Sponsor's proposed indication:

The sponsor proposed to expand the current indication from "treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy" to "treatment of iron deficiency anemia in chronic kidney disease (CKD) patients on erythropoietin".

B. State of Armamentarium for Indication(s)

Approved Products	Dosage and Administration	Population	Wording in indication
Venofer (iron sucrose injection)	100 mg of elemental iron intravenously during each dialysis for 10 sequential dialysis sessions by slow injection: at a rate of 1 mL (20 mg iron) undiluted solution per minute or by infusion: over at least 15 minutes diluted exclusively in a maximum of 100 mL of 0.9% NaCl, immediately prior to infusion.	Adults	"treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy"
Ferrlecit (sodium Ferric Gluconate complex in Sucrose injection)	125 mg of elemental iron intravenously (at a rate of up to 12.5 mg/min) over eight sessions at sequential dialysis by slow injection or infusion over 1 hour diluted in 100 mL of 0.9% sodium chloride.	Adults	"treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental epoetin therapy"

INfed (iron dextran injection)	Adults and Children over 15 kg (33 lbs): Dose (mL) = 0.0442 (Desired Hb-Observed Hb) × LBW (kg) + (0.26 × LBW) Children 5-15 kg (11-33 lbs): Dose (mL) = 0.0442 (Desired Hb-Observed Hb) × W (kg) + (0.26 ×W) Each mL contains 50 mg of elemental iron. A test dose is required before the dosing.	Adults and Pediatrics	"treatment of patients with documented iron deficiency in whom oral administration is unsatisfactory or impossible"

Reviewer's table

C. Important Milestones in Product Development

The sponsor submitted a phase 3 study protocol on May 3, 2000 to expand the current indication to include pre-dialysis CKD patients with iron deficiency anemia. The protocol was reviewed and several recommendations were sent to the sponsor in the Division's letter dated June 28, 2000. These recommendations included advice regarding type of study design and possible control group as stated in the Division's letter comments #3 to #5 as below:

3. Clarify whether the study is designed to show superiority of Venofer over oral iron or equivalence between the two treatments.
4. If the study is designed to show a superiority claim and fails, it will be problematic if you revert to a non-inferiority or equivalence claim. Non-inferiority and equivalence claims require a pre-specified treatment difference margin (delta) in the protocol.
5. We suggest the addition of a placebo plus epoetin treatment arm for the following reasons: a) Oral iron plus epoetin is not approved in the indication sought; b) If Venofer fails to demonstrate Superiority to oral iron plus epoetin it may be tested against placebo plus epoetin; and c) The effectiveness of oral iron may be established by testing against placebo.

In response to the Division's recommendations, the sponsor submitted a 45-day special protocol assessment request on December 6, 2000. In that submission, the sponsor responded to the above recommendations commenting "This study is designed to show superiority of Venofer to oral iron.", "Luitpold Pharmaceuticals, Inc., understands the risk and it is understood that failure to reject the null hypothesis in a superiority claim cannot be construed as proof of equivalence.", "only two arms would be used, as currently planned" and "It is understood that this is a risk; however, the superiority of Venofer over oral iron is the hypothesis of interest."

In that submission, the sponsor also had two questions to the Division including if it is sufficient to use the proposed single study to support approval of an indication for use of Venofer in predialysis patients and "If this study does not show superiority over oral iron but the 200 mg dose is well tolerated in the 78 patients to be studied, will this study, plus supportive data from the published literature be adequate to add 200 mg dosing information to our currently approved existing labeling?". The Division responded in the letter to the sponsor dated January 10, 2001

that acceptability of the proposed single study to support the request indication will be result dependent. A single study must be a large multicenter study providing strong, convincing evidence of efficacy with consistency across primary and secondary endpoints, subgroups, and centers. The study should be independently substantiated with other clinical data. In response to the question about adding a 200 mg dosing regimen to the current labeling, the Division responded "No. Substantial evidence of the safety and efficacy of the proposed dose in the treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental epoetin is required for approval of a new dosage regimen. To add a new dosage regimen to the currently approved labeling, you should conduct an adequate and well-controlled study comparing the proposed dosage regimen to the approved dosage regimen in the same patient population for the currently approved labeling".

The sponsor later submitted protocol amendment on October 15, 2001 to propose to change the primary efficacy endpoints of the study from mean changes in hemoglobin and ferritin from baseline pre-defined in the protocol to "clinical success" (defined as an increase in hemoglobin $\geq$0.8 mg/dL and an increase in ferritin $\geq$ 160 ng/mL from baseline to Day 43) during the study. The Division denied the sponsor's request because a change in the primary endpoint during the study or at the end of the study may potentially bias the study results and the status of study was not provided. The Division suggested that the proposed new analysis could be done as a secondary analysis (Letter dated February 7, 2002).

D. Other Relevant Information

Venofer is marketed in 69 countries currently.

E. Important Issues with Pharmacologically Related Agents

Intravenous iron products have been associated with anaphylactoid reactions. INFeD (iron dextran) has a black boxed warning for anaphylactic-type reactions. Ferrlecit and Venofer have warnings for hypersensitivity reaction.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

No new data were submitted for Chemistry, Animal Pharmacology and Toxicology, Microbiology, and Biopharmaceutics.

See Statistics review.

III. Human Pharmacokinetics and Pharmacodynamics

No new data were submitted for Human Pharmacokinetics and Pharmacodynamics.

IV. Description of Clinical Data and Sources

A. Overall Data

The following material in the NDA submission was reviewed:

- NDA SE1-008 volume M47.1-M47.37, submitted August 15, 2003
- Amendment No. 001, Safety Update, submitted February 20, 2004

B. Tables Listing the Clinical Trials

Studies	Type of trials	Number of patients enrolled	Dose regimen	Control group	Location of the study
1VEN99012	Multi-center, open-label, randomized, concurrent controlled study	102 CKD patients not on dialysis	Venofer 200 mg IV slow injection weekly for 5 doses	Oral iron tablets (Ferrous sulfate) 325 mg three times a day for 29 days	United States

Reviewer's table

C. Post-Marketing Experience

Venofer is currently marketed in 69 countries. Post-marketing safety database established by manufacturer of Venofer [Vifor (international), Inc., Switzerland] since 1992 is available.

D. Literature Review

The sponsor included the summaries of 3 published studies of Venofer in chronic renal failure patients not on dialysis. The sponsor's effort to review the published literature appears adequate.

V. Clinical Review Methods

A. How the Review was Conducted

One clinical trial was submitted and was reviewed for the proposed new indication. The trial and other submitted material were evaluated in the integrated safety summary.

B. Overview of Materials Consulted in Review

The datasets of the one study submitted were examined for the efficacy and safety evaluation.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

No inspection was done for this supplement.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trial was conducted in accordance with accepted ethical standards. Written informed consents were required from all patients in the trial. Independent ethics committees/institutional review boards at all participating centers were required to give permission for these studies.

E. Evaluation of Financial Disclosure

The sponsor certified that there was no financial arrangement with clinical investigators, who conducted the clinical trial (Form FDA 3454).

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

One study (1VEN99012) was submitted to support the indication for treatment of iron deficiency anemia in chronic kidney disease patients not on dialysis.

The study failed to demonstrate that Venofer is superior to oral iron in increasing hemoglobin at Day 43 from baseline in patients with chronic kidney disease not on dialysis (1.0 mg/dL in the Venofer group and 0.7 mg/dL in the oral iron group, $p=0.14$). The study showed a significant difference in an increase in ferritin level at Day 43 from baseline between the Venofer group and the oral iron group (288 ng/mL and -5.1 ng/mL, respectively, $p<0.0001$). However, change in hemoglobin is a more clinically relevant and important endpoint than change in ferritin for treatment of anemia in patients with chronic kidney disease not on dialysis since the main cause of anemia may not be iron deficiency in these patients.

The study showed significant increases in hemoglobin at Day 43 as compared to baseline in both treatment groups ($p<0.02$ in the Venofer group and $p<0.002$ in the oral iron group). Since the majority of patients were epoetin naïve and initiated epoetin treatment at the same time iron therapy was initiated in the study, an increase in hemoglobin from baseline may be due (at least in part) to new use of epoetin therapy in the both treatment groups. This was supported by an increase of hemoglobin (0.7 mg/dL) without an increase of ferritin level (-5.1 ng/mL) in the oral iron group. In a subgroup analysis, in patients with ferritin <100 ng/mL at baseline (20 in the Venofer group and 29 in the oral iron group) there was greater increase in hemoglobin from baseline in the Venofer group as compared to the oral iron group (1.4 g/dL and 0.9 g/dL, respectively, $p=0.046$).

The secondary efficacy analyses had similar findings. The results showed no significant difference in an increase in hematocrit at Day 43 from baseline between the Venofer group and the oral iron group (3.7% and 2.8%, respectively, p=0.12). There was a significant difference in an increase in TSAT at Day 43 from baseline between the Venofer group and the oral iron group (4.5% and 0.5%, respectively, p<0.0001).

It is noteworthy that a significant proportion of randomized patients were not included in the primary efficacy analysis [26 % (14/53) in the Venofer group and 12% (6/49) in the oral iron group)]. There were 9% of patients who discontinued study before the treatment and 17% of patients who did not complete the treatment in the Venofer group as compared to 2% and 10%, respectively, in the oral iron group. These may affect the efficacy and safety results of the study.

There was a notable imbalance in the iron status at baseline between the two treatment groups. Patients with TSAT <20% and ferritin <100 ng/mL were 33% in the Venofer group and 54% in the oral iron group. Also, there was an uneven distribution in age, gender and race between the two treatment groups.

Overall, the results from Study 1VEN99012 do not provide adequate support for the proposed indication for the treatment of iron deficiency anemia in patients with chronic kidney disease not on dialysis. An adequate and well-controlled study to demonstrate the effectiveness of Venofer in terms of an increase in hemoglobin in iron deficiency patients with chronic kidney disease not on dialysis will be needed. The study should be a randomized, parallel groups, controlled study. The study patients should be patients who have received epoetin therapy with a stable dose for at least 3 months before the study and who will maintain the previous epoetin dose as much as possible during the study.

B. General Approach to Review of the Efficacy of the Drug

The sponsor has submitted one study (1VEN99012) to support the new indication. This study was reviewed in detail.

C. Detailed Review of Trials by Indication

One trial was conducted to support the indication for the treatment of iron deficiency anemia in CKD patients not on dialysis.

Study 1VEN99012

Study Protocol

Title of the Study
Comparison of Oral Iron with Intravenous Iron in Patients with Anemia of Chronic Renal Failure not on Dialysis (1VEN99012).

Study Objective

The primary objective of this study was to compare the efficacy and safety of Venofer plus epoetin to oral iron [ferrous sulfate] plus epoetin for managing anemia in patients with CRF not on dialysis.

Study Design
This was an open-label, randomized, concurrent control study. Patients were randomized into the following two groups:

Group A: Ferrous sulfate 325 mg three times a day for 29 days.
Group B: Venofer 200mg by slow injection weekly for 5 doses (on days 1, 8, 15, 22 and 29).

All patients were to receive Epoetin 4000 IU s. c. for 6 doses (on days 1, 8, 15, 22, 29 and 36). An end-of-treatment evaluation was to be on Day 43. All patients were to be followed-up for an additional 3 months.

Study Population
The study was to enroll 92 patients to obtain 78 evaluable patients, 39 per treatment arm.

Inclusion Criteria:

- Male or female patients with pre-ESRD not yet on dialysis, over the age of 18, able to give informed consent.
- Creatinine clearance of < 40 ml/ min.
- Hemoglobin of < 10.5 g/ dl, based on the average of 2 qualifying values drawn on different days.
- TSAT < 25% and a serum ferritin < 300 ng/ml.
- Serum B12 and folate levels above the lower limits of normal.
- No other causes of anemia [systemic lupus erythematosus, rheumatoid arthritis, myeloma, sickle cell, etc].
- Absence of infection, malignancy or surgery in the prior month.
- Expected survival greater than 6 months.

Exclusion Criteria:

- Known sensitivity to any component of ferrous sulfate, Venofer, Procrit® or Epogen® [human albumin, mammalian cell-derived products].
- History of prior intravenous iron or epoetin treatment within the past month.
- Blood transfusion within the last month or anticipated during the study.
- Uncontrolled hypertension.
- Clinically apparent gastrointestinal bleeding.
- Evidence of malnutrition [albumin < 3 g/dl].
- Suffering from concomitant severe diseases of the liver [decompensated], cardiovascular system, severe psychiatric disorders or other conditions which in the opinion of the investigator makes participation unacceptable.
- Serious bacterial, viral or other acute infectious illness [e. g., hepatitis] unless completely resolved at least 4 weeks before inclusion.

- Pregnancy or lactation.
- Asthma.
- Anticipated surgery of any kind during the study other than vascular access surgery.
- Symptomatic HIV positive patients or HIV positive patients on potentially hemosuppressive therapy.
- Expected to undergo dialysis or renal transplant during the study.

Study Treatments
Venofer was supplied as 5 ml vials, containing 100 mg of iron as Fe[III] hydroxide Sucrose complex.

Ferrous sulfate was supplied to patients at each visit as generic tablets [325 mg tablets FeSO4 containing 65 mg elemental iron per tablet] in unit dose packaging. A record of compliance was to be maintained for each patient.

Treatment Phase:
Patients were randomized into the following two groups:

Group A: Ferrous sulfate was administered as 325 mg tablets [65 mg elemental iron] with 8 ounces of tap water orally three times a day for 29 days [Days 1-29]. Total dose of iron administered was to be 5,655 mg of elemental iron.

Group B: Venofer 200 mg was administered by intravenous injection [2 vials, undiluted, 40 mg/min injected over 5 minutes], weekly on Days 1, 8, 15, 22 and 29]. If intolerable adverse events occurred in patients who received Venofer by injection [undiluted], subsequent doses of Venofer were to be diluted in 250 ml of 0.9% NaCl, and administered by infusion over 30-60 minutes. Total dose of iron administered was to be 1000 mg.

Extended Follow-Up Phase:
During the Extended Follow-Up Phase (from Day 50 to Day 114 [3 months post-treatment]), patients who required iron including those in the oral iron group received intravenous iron sucrose (Venofer) and/or epoetin as needed to maintain a hemoglobin level between 11 and 12.5 g/dL, a TSAT of 25-50%, and a ferritin level of 300-500 ng/mL, using a predefined algorithm.

Concomitant Medication
All patients received epoetin 2,000 U subcutaneously on Days 1, 8, 15, 22, 29, and 36. Epoetin was obtained commercially as [redacted]. Prior to Day 43, epoetin doses were held constant; however, doses could have been decreased for patients' safety only, according to pre-defined algorithm.

The route of administration, dose and duration of concomitant medications were to be recorded in the CRFs. No additional iron preparations were to be allowed. After Day 29, no further oral or intravenous iron should be given until after the Day 43 [end of treatment] evaluation.

Efficacy Parameters

The primary efficacy endpoints were the change in hemoglobin concentration and serum ferritin from baseline to Day 43. Mean changes between intravenous iron and oral iron were to be compared.

Secondary measures of efficacy were to be clinical success, the change from baseline to Day 43 in Hct and % TSAT, the number of patients who attain Hb > 11 g/dL during the study, the change from baseline to end of study in epoetin and iron requirements, and change from baseline in quality of life.

Clinical success was defined as an increase of $\geq$ 0.8 g/dL from baseline in hemoglobin and an increase of $\geq$160 ng/mL change from baseline in ferritin at any timepoint during the Treatment Phase.

Safety Assessment
Any untoward medical events (clinical or laboratory), at any dose, experienced by a subject during the course of this clinical trial, whether or not it is related to the investigational product, were to be recorded on the Adverse Event (AE) page of the case report form [CRF].

Statistical Methods
Null hypotheses:
The null hypothesis of interest was that there was no difference in hemoglobin and ferritin change from baseline to Day 43 between oral iron and intravenous iron sucrose. The alternative hypothesis was that there was a difference between the 2 treatment groups in these parameters.

Multiple comparisons/multiplicity:
Since there were 2 primary null hypotheses tested independently in this study, the Hochberg (1988) step-up method was used to control the overall alpha to be 0.05. Based on this method, if the least significant p-value, P(2), was less than or equal to the significance level of 0.05, both hypothesis of interest were rejected; otherwise, P(2) was retained and the other p-value, P(1), was compared with the significance level of 0.025.

Sample size determination:
The size of study samples was estimated based on 2 null hypotheses, each tested at the 2.5% significance level. A sample size of 39 patients was also estimated to be adequate to detect a difference in the change from baseline in serum ferritin level of 160 ng/ml, given a 2-sided t-test with 2.5% significance level, and 80% power. A common standard deviation (SD) is assumed to be 220 ng/ml, based upon a previous study. Due to a projected 15% non-evaluability rate, a total sample size of 92 patients was to be required.

Analysis of efficacy:
The primary efficacy endpoints are the change in Hb from baseline to Day 43 and the change in ferritin from baseline to Day 43. The efficacy of intravenous iron versus oral iron will be evaluated by an analysis of covariance (ANCOVA) model. The covariates evaluated were baseline hemoglobin, baseline ferritin, baseline TSAT, baseline hematocrit, study center, epoetin status, age group, gender, and race. The model included treatment effect, covariates, and

interaction between the treatment and each of the covariates. Covariates and their interactions were considered statistically significant if $p < 0.10$. This step was done separately for each of the 2 primary efficacy parameters..

A final model was identified by including treatment effect and all statistically significant covariates and interactions. The final model was used to estimate the overall treatment effect and the nominal p-values for testing the differences between the 2 groups. Least squares means (LS-means) for each treatment, differences in the LS-means between the groups, and 95% CI for the LS-means and for the LS-means difference were also provided. In case of significant treatment by center interaction, the nature of the interaction will be explored. Step 2 was done separately for each of the 2 primary efficacy parameters.

For the secondary endpoints: changes from baseline in Hct, %TSAT, and changes in epoetin and iron dose requirements were to be assessed by the same method as the primary efficacy endpoint. The proportion of patients who attain the target Hb > 11 g/dL after treatment were to be assessed by Cochran-Mantel-Haenszel test in corporate with the effect of center. Improvement in quality of life was to be assessed by descriptive statistics.

For each efficacy endpoint, summaries of absolute values and changes from baseline by treatment group and visit were to be presented.

Analysis of safety:
Descriptive statistics were to be provided for all safety parameters at each study visit. Ninety-five percent [95%] confidence intervals were to be provided for the change from baseline to last on-study visit for the hematological and clinical chemistry parameters. Adverse events during the treatment period were to be compared to those reported during the screening period.

Handling of dropouts or missing Data:
Patients who withdrew from the study were included in the analysis up to the time point when the patient was withdrawn. Missing data were not imputed unless otherwise specified for a specific parameter. The patients with missing data were summarized in a separate category where appropriate.

Changes in the Conduct of the Study or Planned Analyses

Changes to the Protocol
One amendment and 1 administrative change were made to the protocol. All patients were enrolled under Amendment #1 of the protocol.

Amendment #1, dated 13 September 2000, incorporated the following changes:

- Changed dosage of epoetin from 4000 U subcutaneously weekly to 2000 U subcutaneously weekly.
- Added package insert for ferrous sulfate to Appendix.

- Added 2 qualifying baseline blood samples for hematology and iron indices to be drawn. Additionally, the qualifying baseline hemoglobin values must have averaged less than 10.5 g/dL and may not have differed from each other by more than 0.5 g/dL.
- Added end-of-treatment clinical chemistry evaluation performed on Day 43.
- Removed stool hemoccult requirement.
- Added hematologic parameter evaluations on Day 71 and Day 100 (biweekly throughout the study).
- Added a minimum of 2 weeks between epoetin dose adjustments.
- Clarified that [redacted] rather than Luitpold Pharmaceuticals, Inc., was to provide sites with a patient randomization number.
- Changed ferrous sulfate administration to 1 hour before meals.
- Changed Venofer administration from 20 mg/min injected over 5-10 min to 40 mg/min injected over 5 minutes.
- Added the equivalent increase in hemoglobin (2.6 g/dL) to increased hematocrit definition.
- Added that worsening renal failure was not to be considered an adverse event.
- Added that the statistical assumptions for an ANCOVA model would be verified. If the data did not meet the underlying assumptions, the analyses would be based on ranks.
- Clarified the statistical analyses to be performed in case of a significant treatment-by-center interaction.
- Made various wording changes.

Administrative Change # 1, dated 21 June 2001, incorporated the following changes:

- Added package insert for Venofer to Appendix.
- Added a row for clinical chemistry to tables of scheduled evaluations on Day 43. Changed [redacted] as the provider to the sites for patient randomization numbers.
- Removed Day 29 hemoglobin, ferritin, and TSAT measurements.
- Clarified that patients could have continued to receive intravenous iron sucrose (Venofer) and epoetin at weekly visits on or after the Day 43 evaluation.
- Added clinical chemistry to the list of end-of-treatment procedures.
- Clarified that the Investigator was to document his/her opinion of the relationship of the event to the study drugs (epoetin and/or Venofer; epoetin and/or oral iron).
- Added another contact for serious adverse event reporting.
- Made various wording changes.

Changes in the Planned Analyses

Clinical success was added as a secondary efficacy endpoint during the study. Clinical success was defined as an increase of $\geq$ 0.8 g/dL from baseline in hemoglobin and an increase of $\geq$160 ng/mL change from baseline in ferritin at any timepoint during the Treatment Phase.

Several other supportive analyses were performed for the presentation of efficacy results. These analyses included the determination of the maximum level of hemoglobin attained during the

Treatment and Extended Follow-Up Phases, a change in criteria for patients in the Per Protocol Population, and modifications of the definitions and nomenclature of anaphylaxis and allergic reactions. Supplement analyses included the proportions of patients who met the change in hemoglobin/TSAT criteria, the hemoglobin/ferritin/TSAT criteria, and the ferritin/TSAT criteria.

Although not specified in the protocol, a secondary endpoint of clinical success was described in the Statistical Analysis Plan and presented in the results of efficacy. Although not specified in the protocol or the Statistical Analysis Plan, an analysis using the MANOVA option in the PROC GLM procedure, considering the percent changes from baseline to Day 43 in hemoglobin and ferritin values as 2 dependent variables and treatment as the factor in the model, was performed.

Study Patients

Patient Disposition

A total of 102 patients were randomized at 16 centers in the study. Of these 102 patients, 6 (1 in the oral iron group and 5 in the Venofer group) were discontinued from the study prior to receiving study medication and were excluded from the efficacy and safety analyses. A total of 96 patients (48 in the oral iron group and 48 in the Venofer group) received at least one dose of study medication. The study was conducted between February 23, 2001 and May 30, 2002.

Reviewer's comments: Six (5.9%) patients discontinued from the study after randomization. The sponsor did not provide the reasons for discontinuations in these patients.

A summary of patient disposition is presented in the table below.

Table 5.1a Patient Disposition and Study Termination During the Treatment Phase

	Oral Iron	Venofer®	Total
All Randomized Patients	49	53	102
Patients Discontinued Prior to Receiving Study Medication	1	5	6
Patients Treated in Treatment Phase	48	48	96
Patients Discontinued From Treatment Phase	4 (8.3%)	9 (18.8%)	13 (13.5%)
Reasons for Discontinuation From Treatment Phase:			
Adverse Event	1 (2.1%)	5 (10.4%)	
Dialysis	0	1 (2.1%)	
Blood Loss Requiring Transfusion	0	1 (2.1%)	
Selection Criteria/Study Compliance	1 (2.1%)	0	
Lost to Follow-Up	1 (2.1%)	1 (2.1%)	
Patient Request	1 (2.1%)	0	
Other	0	1 (2.1%)	
Patients Who Completed Treatment Phase	44 (91.7%)	39 (81.3%)	83 (86.5%)
Patients Who Completed Treatment Phase but did not enter Extended Follow-Up Phase	1 (2.1%)	4 (8.3%)	5 (5.2%)
Patient Choice	1 (2.1%)	3 (6.3%)	
Other	0	1 (2.1%)	

Cross-reference: Appendix Table 1.1 and Appendix Listing 1

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 48

Among patients who received at least one dose of study drugs, 4 (8.3%) patients in the oral iron group and 9 (18.8%) patients in the Venofer group did not complete the Treatment Phase. The reasons for treatment discontinuation in the two groups are listed in the table above. The main reason in the Venofor group was due to adverse events (5 patients, 10.4%).

Reviewer's comments: Nearly 20% of patients did not complete treatment phase in Venofer group and most of these discontinuations (5 patients, 10.4%) were due to adverse events as compared to 8.3% of patients in the oral iron group not completing the treatment phase and only one discontinuation (2.1%) being due to adverse event.

Four patients (1 in the oral iron group and 3 in the Venofer group) completed the Treatment Phase but chose not to enter the Extended Follow-Up Phase of the study. Additionally, 1 Venofer patient completed the Treatment Phase but did not enter the Extended Follow-Up Phase due to the start of dialysis.

A summary of patient disposition during the Extended Follow-up phase is presented in table below.

Table 5.1b Patient Disposition and Study Termination During Extended Follow-Up Phase

	Oral Iron	Venofer®	Total
Patients Enrolled in Extended Follow-Up Phase	43	35	78
Patients Discontinued From Extended Follow-Up Phase	6 (14.0%)	7 (20.0%)	13 (16.7%)
Reasons for Discontinuation From Extended Follow-Up Phase:			
Adverse Event	2 (4.7%)	3 (8.6%)	
Dialysis	2 (4.7%)	3 (8.6%)	
Lost to Follow-Up	1 (2.3%)	0	
Patient Request	0	1 (2.9%)	
Other	1 (2.3%)	0	
Patients Who Completed Extended Follow-Up Phase	37 (86.0%)	28 (80.0%)	65 (83.3%)

Cross-reference: Appendix Table 1.1 and Appendix Listing 1

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 49

Seventy-eight patients (43 in the oral iron group and 35 in the Venofer group) were enrolled into the Extended Follow-Up Phase of the study. Thirty-seven (86.0%) of the 43 patients in the oral iron group and 28 (80.0%) of the 35 patients in the Venofer group completed the Extended Follow-Up Phase. Six patients in the oral iron group (2 due to adverse events, 2 requiring dialysis, 1 lost to follow-up, and 1 due to non-evaluable end-of-treatment labs) and 7 patients in the Venofer group (3 due to adverse events, 3 requiring dialysis, and 1 due to patient request) did not complete the Extended Follow-Up Phase,

Protocol Deviations

Four patients were misrandomized with respect to their history of epoetin use. Two patients in the Venofer group were epoetin naive but were randomized to the prior epoetin use strata. Additionally, one patient in the Venofer group and one patient in the oral group had a history of prior epoetin use but were randomized to the epoetin naive strata.

Eleven patients in the oral iron group and 13 patients in the Venofer group had violations of inclusion/exclusion criteria, but were granted exceptions by the sponsor to participate in the study. The most common violation for which exception was granted was the inclusion criterion of creatinine clearance < 40 mL/min.

A total of 8 patients (4 in the oral iron group and 4 in the Venofer group) were identified as having violated the protocol by receiving concomitant iron medication, supplemental epoetin, and/or blood transfusions during Days 1 to 43. These patients were excluded from the efficacy analyses of the Per Protocol Population.

RESULTS

Data Sets Analyzed

All patients (N= 96) who received any amount of study medication and had post-treatment safety information were included in the Safety Evaluable Population.

All patients (N= 96) who received any amount of study medication and had baseline hemoglobin values < 10.5 g/dL (or were granted exceptions for entry by the sponsor) were included in the Intent-to-Treat Population.

Four patients in each of the treatment groups received prohibited medications during the Treatment Phase and were excluded from the Per Protocol Population. A summary of the datasets analyzed is presented in the table below.

Table 6.1a Datasets Analyzed

Population	Oral Iron (N=48)	Venofer® (N=48)
Patients Treated	48 (100%)	48 (100%)
Safety Evaluable Population	48 (100%)	48 (100%)
Intent-to-Treat Population	48 (100%)	48 (100%)
Per Protocol Population	44 (91.7%)	44 (91.7%)
Reasons Excluded from Per Protocol Population:		
Protocol Violation (received excluded concomitant treatment)	4 (8.3%)	4 (8.3%)

Cross-reference: Appendix Tables 1.2 and 1.3 and Appendix Listing 3

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 50

Demographic and Baseline Characteristics

Demographic Characteristics

A summary of the demographic characteristics of the treatment groups is presented in the table below.

Table 6.2a Demographic Characteristics at Baseline (Safety Evaluable Population)

Demographic Characteristic	Oral Iron (N=48)	Venofer® (N=48)
Age (years)		
<65	29 (60.4%)	22 (45.8%)
≥65	19 (39.6%)	26 (54.2%)
Overall Mean (SD)	60 (14.0)	62 (14.4)
Median	59	65
Minimum - Maximum	28 – 90	27 – 91
Gender		
Male	14 (29.2%)	19 (39.6%)
Female	34 (70.8%)	29 (60.4%)
Race		
Black	14 (29.2%)	11 (22.9%)
Caucasian	21 (43.8%)	18 (37.5%)
Other	13 (27.1%)	19 (39.6%)
Hispanic	11 (22.9%)	17 (35.4%)
Asian	1 (2.1%)	1 (2.1%)
Philippino	1 (2.1%)	1 (2.1%)
Weight (kg)	(N=46)	(N=48)
Mean (SD)	84.0 (19.2)	84.2 (24.3)
Median	82.6	81.9
Minimum - Maximum	49.1 - 129.0	39.9 - 153.0

SD=Standard Deviation

Cross-reference: Appendix Table 2.1.1 and Appendix Listing 4.1

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 51

No statistically significant differences were observed between the 2 treatment groups in the Safety Evaluable Population for any of the demographic or baseline characteristics. Mean age was 60 years in the oral iron group and 62 years in the Venofer group. The majority of the patients in both treatment groups were female (70.8% in the oral iron group and 60.4% in the Venofer group). The oral iron group was comprised primarily of Caucasian patients (43.8%) while the Venofer group was comprised primarily of "other" races (Hispanic 35.4%, Asian 2.1%, and Philippino 2.1 %).

Reviewer's comments: Although no statistical significance was found between the two treatment groups for age, gender and race, the table shows that the patients in the Venofer group were older, more males and more other races than in the oral iron group. The impact of these imbalances on the efficacy results is not clear.

Baseline epoetin use and iron index

A summary of the baseline characteristics of the treatment groups is presented in the table below.

Table 6.2b Baseline Characteristics (Safety Evaluable Population)

Baseline Characteristic	Oral Iron (N=48)	Venofer® (N=48)
Epoetin Status		
Naïve	43 (89.6%)	40 (83.3%)
Previous User	5 (10.4%)	8 (16.7%)
Baseline Hemoglobin (g/dL)		
Mean (SD)	9.7 (0.8)	9.8 (0.6)
Median	10.0	9.9
Minimum - Maximum	7.5 - 10.6	7.7 - 10.7
Baseline TSAT (%)		
Mean (SD)	15.6 (5.4)	16.6 (4.9)
Median	14.9	16.7
Minimum - Maximum	4.7 - 27.4	7.9 - 28.6
<20%	39 (81.3%)	36 (75.0%)
Baseline Ferritin (ng/mL)		
Mean (SD)	103.0 (77.0)	125.0 (77.5)
Median	78.8	131.0
Minimum - Maximum	4.2 - 296.0	11.4 - 343.0
<100 ng/mL	31 (64.6%)	21 (43.8%)
Baseline TSAT <20% and Ferritin <100 ng/mL	26 (54.2%)	16 (33.3%)
Prior Iron Intolerance		
Yes	1 (2.1%)	0
Iron Dextran	1 (2.1%)	0

SD=Standard Deviation

Cross-reference: Appendix Table 2.1.1 and Appendix Listing 4.2

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 52

The majority of the patients in both treatment groups were epoetin-naive (89.6% in the oral iron group and 83.3% in the Venofer group). Mean hemoglobin and TSAT values at baseline were similar between the oral iron group and the Venofer group. The proportion of patients with a baseline TSAT < 20% was 81.3% in the oral iron group and 75.0% in the Venofer group. Mean ferritin at baseline was higher in the Venofer group (125.0 ng/ mL) than in the oral iron group (103.0 ng/mL). The proportion of patients with a baseline ferritin < 100 ng/mL was 64.6% in the oral iron group and 43.8% in the Venofer group. Overall, 54.2% of the patients in the oral iron group and 33.3% of the patients in the Venofer group had a baseline TSAT < 20% and ferritin < 100 ng/mL.

Reviewer's comments: Initiation of epoetin therapy in the majority of study patients at the same time as Venofer treatment was started in the study may have confounded the study results because epoetin may itself increase hemoglobin. This will affect the comparison in hemoglobin between the baseline and the follow-up. However, the comparison between the Venofer group and the oral iron group in the change in hemoglobin from baseline may not be affected much, since the distribution of new users of epoetin between the two groups is fairly even. It was noted that there was an imbalance in the iron status at baseline between the Venofer and oral iron groups. More patients had iron deficiency (TSAT<20% and ferritin<100 ng/mL) at baseline in the oral iron group than in the Venofer group even though the mean hemoglobin levels were similar between the two treatment groups. This suggests that anemia in patients in the oral iron group may have been more likely due to iron deficiency than in patients in the Venofer group. This could bias the results in favor of oral iron group.

One oral iron patient had a prior history of iron intolerance (iron dextran). This patient's primary symptom associated with iron dextran administration was dyspnea. No other patients reported a prior history of iron intolerance.

No statistically significant differences were observed between the 2 treatment groups in the Intent-to-Treat or Per Protocol Populations for any of the demographic or baseline characteristics.

Medical History/Concomitant Illness

All of the patients had ongoing medical conditions at study entry. In addition to chronic renal insufficiency/failure, significant medical histories reported included hematologic/oncologic conditions (primarily anemia), cardiovascular conditions (primarily hypertension), and endocrine/metabolic conditions (primarily diabetes mellitus).

Prior Medication

The majority of the patients in both treatment groups were receiving medications prior to study participation. The types of medications received prior to study participation were similar between the treatment groups.

Concomitant Medications

The majority of the patients in both treatment groups received concomitant medications during the Treatment Phase of the study. The types of medications received during the Treatment Phase were similar between the treatment groups. The majority of the patients received concomitant medications during the Extended Follow-Up Phase of the study. The types of medications received during the Extended Follow-Up Phase were similar between the treatment groups.

Treatment Compliance

During the Treatment Phase, mean treatment compliance was lower in the oral iron group (85.5%) compared with the Venofer group (95.0%). The proportion of patients who were at least 80% compliant with the treatment regimen was 83.3% in the oral iron group and 93.8% in the Venofer group. A summary of treatment compliance during the Treatment Phase is presented in The table below.

Table 6.3a Summary of Treatment Compliance During the Treatment Phase (Safety Evaluable Population)

% Compliance	Oral Iron (N=48)	Venofer® (N=48)
Mean (SD)	85.5 (21.95)	95.0 (15.62)
95% Confidence Interval of Mean	79.3, 91.7	90.6, 99.5
Median	93.1	100.0
Minimum - Maximum	1.1 - 100.0	20.0 - 100.0
Patients ≥80% Compliant	40 (83.3%)	45 (93.8%)

Cross-reference: Appendix Table 5.2 and Appendix Listing 8.1

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 54

Reviewer's comments: As expected, the treatment noncompliance was lower in the oral iron group as compared to the Venofer group. This may affect the results in favor of Venofer group.

Efficacy Results

Primary Efficacy Analysis

Hemoglobin

Intent-to-Treat Population

A summary of the mean changes from baseline to each visit in hemoglobin during the Treatment and Extended Follow-Up Phases of the study is presented in the table below.

Table 6.4a Summary of Mean Changes From Baseline to Each Visit in Hemoglobin (g/dL) During the Treatment and Extended Follow-Up Phases (Intent-to-Treat Population)

	Treatment Phase							
	Oral Iron (N=48)				Venofer® (N=48)			
	N	BL (SD)	Change from BL (SD)	p-value[a]	N	BL (SD)	Change from BL (SD)	p-value[a]
Day 15	45	9.8 (0.70)	0.3 (0.52)	0.002	47	9.8 (0.58)	0.3 (0.86)	0.017
Day 36	44	9.8 (0.70)	0.6 (0.79)	<0.0001	41	9.8 (0.60)	0.7 (1.09)	<0.0001
Day 43	43	9.7 (0.71)	0.7 (0.97)	<0.0001	39	9.9 (0.60)	1.0 (0.98)	<0.0001
LS Means 95% CI	0.7 0.4, 1.0				1.0 0.7, 1.3			
	Venofer® - Oral Iron LS Mean: 0.3 95% CI: -0.1, 0.7							
p-value[b]	p=0.1370							
	Extended Follow-Up Phase							
	Venofer®[c] (N=78)							
	N	Baseline (SD)	Change from Baseline (SD)	p-value[a]				
Day 57	75	9.8 (0.68)	1.1 (1.00)	<0.0001				
Day 71	72	9.8 (0.69)	1.3 (1.17)	<0.0001				
Day 86	68	9.8 (0.69)	1.5 (1.02)	<0.0001				
Day 100	65	9.8 (0.69)	1.7 (1.06)	<0.0001				
Day 114	64	9.8 (0.69)	1.6 (1.09)	<0.0001				

BL = baseline; SD = standard deviation; LS = least squares; CI = confidence interval

a p-value calculated from paired sample t-test at alpha = 0.05.

b p-value for the difference in the LS-means between the 2 groups.

c Patients could have received Venofer® and/or epoetin during the Extended Follow-Up Phase as needed to maintain a hemoglobin level between 11 and 12.5 g/dL, a TSAT of 25-50% and a ferritin level of 300-500 ng/mL.

Cross-reference: Appendix Tables 3.1.1.1, 3.1.1.2, and 3.1.1.3 and Appendix Listings 7.1 and 7.2

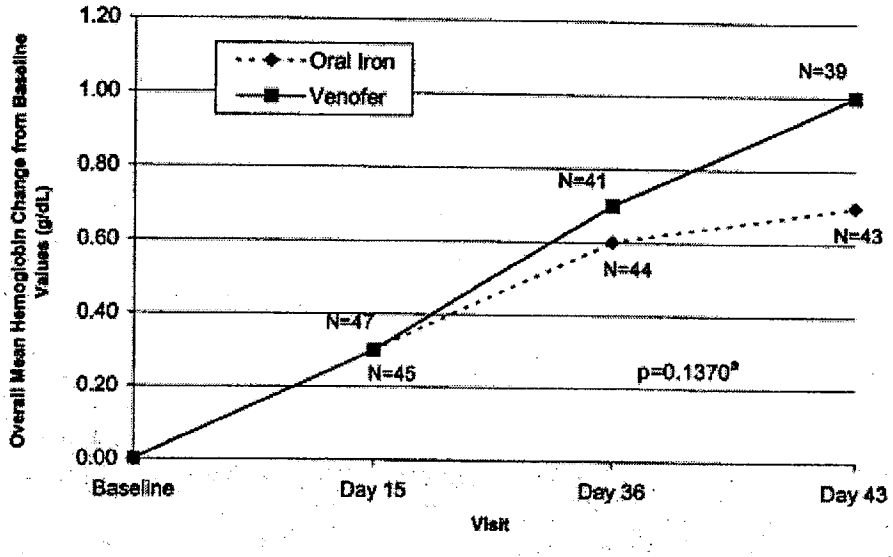
Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 56

During the Treatment Phase, statistically significant mean increases from baseline in hemoglobin values were observed at each visit (Days 15, 36, and 43) in the Venofer group. The mean change from baseline to Day 43 in hemoglobin was 1.0 g/dL.

Statistically significant mean increases from baseline in hemoglobin values were also observed at each visit during the Treatment Phase (Days 15, 36, and 43) in the oral iron group. The mean change from baseline to Day 43 in hemoglobin was 0.7 g/dL.

The difference between the treatment groups for the mean change from baseline to Day 43 in hemoglobin was not statistically significant.

Mean changes from baseline in hemoglobin values during the Treatment Phase are presented in the figure below.



a p-value calculated from LS means.
Cross-Reference: Appendix Tables 3.1.1.1 and 3.1.1.2

Figure 6.4a Mean Changes From Baseline in Hemoglobin Values Over Time (Intent-to-Treat Population)

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 55

Reviewer's comments: The study showed significant increase in hemoglobin from baseline in Venofer-treated and oral-iron-treated patients. The mean increase in hemoglobin from baseline in the Venofer group was slightly higher than that in the oral iron groups but the difference between the two groups was not significant (1.0 mg/dL vs. 0.7 mg/dL, p=0.14). The increase in hemoglobin over time in both groups may largely be attributed to new use of epoetin therapy.

During the Extended Follow-Up Phase, statistically significant mean increases from baseline in hemoglobin values were observed at each visit. Mean changes from baseline across visits in hemoglobin values ranged from 1.1 g/dL to 1.7 g/dL.

Per Protocol Population

In the Per Protocol Population, analyses of mean changes from baseline in hemoglobin values were generally similar to those observed in the Intent-to-Treat Population. No statistically

significant difference was observed between the treatment groups in the mean change from baseline to Day 43 in hemoglobin values.

Ferritin

Intent-to-Treat Population

A summary of the mean changes from baseline to each visit in ferritin during the Treatment and Extended Follow-Up Phases of the study is presented in the table below.

Table 6.4b Summary of Mean Changes From Baseline to Each Visit in Ferritin (ng/mL) During the Treatment and Extended Follow-Up Phases (Intent-to-Treat Population)

	Treatment Phase							
	Oral Iron (N=48)				Venofer® (N=48)			
	N	BL (SD)	Change from BL (SD)	p-value[a]	N	BL (SD)	Change from BL (SD)	p-value[a]
Day 15	2	40.9 (34.15)	13.6 (8.70)	0.270	5	177 (84.18)	247 (133.4)	0.014
Day 36	45	104 (79.00)	2.8 (41.69)	0.656	42	113 (67.60)	325 (205.9)	<0.0001
Day 43	44	104 (79.79)	-5.1 (36.81)	0.365	39	110 (66.68)	288 (163.7)	<0.0001
LS Means 95% CI	-5.58 -35.04, 23.88				283.79 252.49, 315.10			
	Venofer® - Oral Iron LS Mean: 289.37 95% CI: 246.39, 332.36							
p-value[b]	p<0.0001							
	Extended Follow-Up Phase							
	Venofer®[c] (N=78)							
	N	Baseline (SD)	Change from Baseline (SD)	p-value[a]				
Day 57	75	108 (73.13)	230 (181.6)	<0.0001				
Day 71	10	126 (78.12)	391 (179.8)	<0.0001				
Day 86	69	108 (75.76)	332 (242.4)	<0.0001				
Day 100	20	101 (71.13)	354 (128.8)	<0.0001				
Day 114	64	106 (77.64)	358 (181.2)	<0.0001				

BL = baseline; SD = standard deviation; LS = least squares; CI = confidence interval

a p-value calculated from paired-sample t-test at alpha = 0.05.

b p-value for the difference in the LS-means between the 2 groups.

c Patients could have received Venofer® and/or epoetin during the Extended Follow-Up Phase as needed to maintain a hemoglobin level between 11 and 12.5 g/dL, a TSAT of 25-50% and a ferritin level of 300-500 ng/mL.

Cross-reference: Appendix Tables 3.1.2.1, 3.1.2.2, and 3.1.2.3 and Appendix Listings 7.1 and 7.2

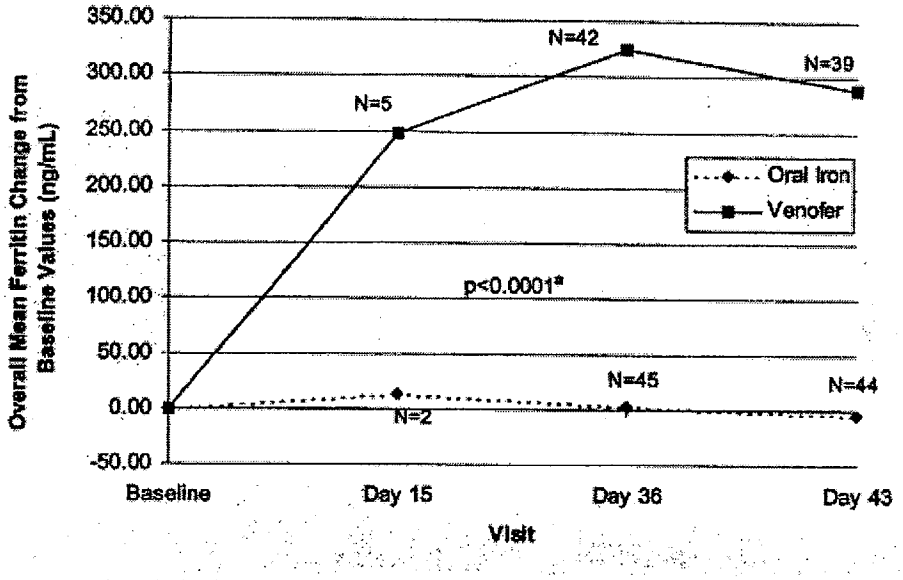
Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 58

During the Treatment Phase, the Venofer group had statistically significant mean increases from baseline in ferritin values at each visit (Days 15, 36, and 43). The mean change from baseline to Day 43 in ferritin was 288.0 ng/mL.

No statistically significant changes from baseline in ferritin values were noted in the oral iron group at any visit during the Treatment Phase (Days 15, 36, and 43). The mean change from baseline to Day 43 in ferritin was -5.1 ng/mL.

The difference between the treatment groups in mean change from baseline to Day 43 in ferritin was statistically significant ($p< 0.001$).

Mean changes from baseline in ferritin values during the Treatment Phase is shown in the figure below.



a p-value calculated from LS means.
Cross-Reference: Appendix Tables 3.1.2.1 and 3.1.2.2

Figure 6.4b Mean Changes From Baseline in Ferritin Values Over Time (Intent-to-Treat Population)

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 57

Reviewer's comments: The study showed a significant difference in the mean changes from baseline in ferritin level between the Venofer and oral iron treatments ($p<0.001$). Above results suggest that Venofer was more effective in terms of delivery iron than oral iron in study patients. However, this highly significant difference in ferritin levels was not reflected in the mean changes in hemoglobin between the two treatments. The results showed that the mean ferritin level in the oral iron group was not changed from the baseline despite the oral iron supplement for almost a month. This suggests that the increase in hemoglobin in the oral iron group was more likely due to starting of epoetin use rather than use of oral iron.(This possibility was further suggested by the fact that 89.6% of patients in the oral iron group and 83.3% of patients in the Venofer group were epoetin-naïve in the study). If this is the case, then in the Venofer group, only 0.3 mg/dL (1.0 mg/dL in the Venofer group - 0.7 mg/dL in the oral iron group) of increase in hemoglobin from baseline can be attributed to iron supplied by Venofer 200 mg for 5 doses.

During the Extended Follow-Up Phase, statistically significant mean increases from baseline in ferritin values were observed at each visit. Mean changes from baseline across visits in ferritin values ranged from 230.0 ng/mL to 391.0 ng/mL.

Per Protocol Population

In the Per Protocol Population, analyses of mean changes from baseline in ferritin values were generally similar to those observed in the Intent-to-Treat Population. A statistically significant difference was observed between the treatment groups in the mean change from baseline to Day 43 in ferritin values ($p<0.001$), with a greater increase in ferritin values observed in the Venofer group (292.0 ng/mL) compared to the oral iron group (-2.4 ng/mL).

Secondary Efficacy Analyses

The secondary efficacy analyses were the proportions of patients who achieved clinical success, changes from baseline to Day 43 in hematocrit and TSAT, and the proportions of patients who attained hemoglobin > 11.0 g/dL during the study.

Clinical Success

Intent-to-Treat Population

In the Treatment Phase, 30 (62.5%) of the 48 patients in the Venofer group achieved clinical success (defined as ≥ 0.8 g/ dL change from baseline in hemoglobin and ≥160 ng/mL change from baseline in ferritin at any timepoint during the Treatment Phase), while none of the patients in the oral iron group met the criteria for clinical success. When evaluated according to visit, 6.3% of the patients in the Venofer group had achieved clinical success by Day 15, 35.4% had achieved clinical success by Day 36, and 62.5% had achieved clinical success by Day 43. A summary of the proportions of patients who achieved clinical success during the Treatment Phase is presented in the table below.

Table 6.4c Summary of Proportions of Patients Who Achieved Clinical Success Overall and by Visit During the Treatment Phase (Intent-to-Treat Population)

	Oral Iron (N=48)	Venofer® (N=48)
Overall	0 (0%)	30 (62.5%)
By Visit	n/N (%)[a]	
By Day 15	N/A	3/48 (6.3%)
By Day 36	N/A	17/48 (35.4%)
By Day 43	N/A	30/48 (62.5%)

a n = patients who attained ≥0.8 g/dL hemoglobin change from baseline and ≥160 ng/mL ferritin change from baseline at any timepoint during the Treatment Phase. N = total number of patients who had data.

Cross-reference: Appendix Tables 3.2.1.1 and 3.2.1.3a and Appendix Listing 7.1

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 60

Reviewer's comments: That no patient in the oral iron group achieved "clinical success" was due to the fact that no patient had >160 ng/mL change from baseline in ferritin at any timepoint during the treatment phase. There were 48% (23/48) of patients who achieved >0.8 mg/dL change from baseline in hemoglobin in the oral iron group by Day 43 based on the sponsor's data in the table 3.2.1.3.b in Volume 5, page 53.

Per Protocol Population

In the Per Protocol Population, analyses of clinical success were similar to those observed in the Intent-to-Treat Population. Overall, 68.2% of the patients in the Venofer group achieved clinical success, while none of the patients in the oral iron group met the criteria for clinical success.

Hematocrit

Intent-to-Treat Population

During the Treatment Phase, statistically significant mean increases from baseline in hematocrit values were observed at each visit (Days 15, 36, and 43) in the Venofer group. The mean change from baseline to Day 43 in hematocrit was 3.7%.

Statistically significant mean increases from baseline in hematocrit values were also observed at each visit during the Treatment Phase (Days 15, 36, and 43) in the oral iron group. The mean change from baseline to Day 43 in hematocrit was 2.8%.

The difference between the treatment groups for the mean change from baseline to Day 43 in hematocrit was not statistically significant.

A summary of the mean changes from baseline to each visit in hematocrit during the Treatment and Extended Follow-Up Phases of the study is presented in the table below.

Table 6.4d Summary of Mean Changes From Baseline to Each Visit in Hematocrit (%) During the Treatment and Extended Follow-Up Phases (Intent-to-Treat Population)

	Treatment Phase							
	Oral Iron (N=48)				Venofer® (N=48)			
	N	BL (SD)	Change from BL (SD)	p-value[a]	N	BL (SD)	Change from BL (SD)	p-value[a]
Day 15	45	30.6 (2.20)	1.0 (1.76)	<0.0001	47	31.0 (2.11)	1.5 (2.61)	<0.0001
Day 36	44	30.6 (2.23)	2.6 (2.56)	<0.0001	41	31.0 (2.04)	2.9 (3.71)	<0.0001
Day 43	43	30.4 (2.13)	2.8 (3.01)	<0.0001	39	31.2 (2.08)	3.7 (3.12)	<0.0001
LS Means 95% CI	2.67 1.78, 3.57				3.70 2.75, 4.65			
	Venofer® - Oral Iron LS Mean: 1.03 95% CI: -0.29, 2.34							
p-value[b]	p=0.1237							
	Extended Follow-Up Phase							
	Venofer®[c] (N=78)							
	N	Baseline (SD)	Change from Baseline (SD)	p-value[a]				
Day 57	75	30.7 (2.16)	3.7 (3.07)	<0.0001				
Day 71	72	30.8 (2.19)	4.3 (3.40)	<0.0001				
Day 86	68	30.7 (2.20)	5.1 (3.08)	<0.0001				
Day 100	65	30.7 (2.25)	5.3 (3.25)	<0.0001				
Day 114	64	30.6 (2.23)	5.2 (3.41)	<0.0001				

BL = baseline; SD = standard deviation; LS = least squares; CI = confidence interval

a p-value calculated from paired-sample t-test at alpha = 0.05.

b p-value for the difference in the LS-means between the 2 groups.

c Patients could have received Venofer® and/or epoetin during the Extended Follow-Up Phase as needed to maintain a hemoglobin level between 11 and 12.5 g/dL, a TSAT of 25-50% and a ferritin level of 300-500 ng/mL.

Cross-reference: Appendix Tables 3.2.2.1, 3.2.2.2, and 3.2.2.3 and Appendix Listing 10.1

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 62

During the Extended Follow-Up Phase, statistically significant mean increases from baseline in hematocrit values were observed at each visit. Mean changes from baseline across visits in hematocrit values ranged from 3.7% to 5.3%.

Per Protocol Population

In the Per Protocol Population, analyses of mean changes from baseline in hematocrit values were generally similar to those observed in the Intent-to-Treat Population. No statistically significant difference was observed between the treatment groups in the mean change from baseline to Day 43 in hematocrit values.

TSAT

Intent-to-Treat Population

During the Treatment Phase, statistically significant mean increases from baseline in TSAT values were observed at Days 36 and 43 in the Venofer group. The mean change from baseline to Day 43 in TSAT values was 4.5%.

No statistically significant changes from baseline in TSAT values were noted in the oral iron group at any visit during the Treatment Phase (Days 15, 36, and 43). The mean change from baseline to Day 43 in TSAT was 0.5%.

The difference between the treatment groups for the mean change from baseline to Day 43 in TSAT was statistically significant ($p < 0.001$).

A summary of the mean changes from baseline to each visit in TSAT during the Treatment and Extended Follow-Up Phases of the study is presented in the table below.

Table 6.4e Summary of Mean Changes From Baseline to Each Visit in TSAT (%) During the Treatment and Extended Follow-Up Phases (Intent-to-Treat Population)

	Treatment Phase							
	Oral Iron (N=48)				Venofer® (N=48)			
	N	BL (SD)	Change from BL (SD)	p-value[a]	N	BL (SD)	Change from BL (SD)	p-value[a]
Day 15	2	15.3 (9.48)	2.7 (0.92)	0.150	5	15.0 (5.70)	1.9 (5.47)	0.484
Day 36	45	15.3 (5.30)	2.1 (7.46)	0.069	42	16.8 (4.88)	5.1 (8.13)	<0.0001
Day 43	44	15.3 (5.35)	0.5 (5.74)	0.567	39	16.9 (5.05)	4.5 (7.13)	<0.0001
LS Means 95% CI	-0.13 -1.69, 1.42				5.25 3.58, 6.91			
	Venofer® - Oral Iron LS Mean: 5.38 95% CI: 3.10, 7.66							
p-value[b]	p<0.0001							
	Extended Follow-Up Phase							
	Venofer®[c] (N=78)							
	N	Baseline (SD)	Change from Baseline (SD)	p-value[a]				
Day 57	75	16.1 (5.18)	4.5 (6.80)	<0.0001				
Day 71	10	17.7 (5.82)	6.2 (6.82)	0.018				
Day 86	68	15.8 (5.09)	7.3 (6.26)	<0.0001				
Day 100	20	14.6 (4.51)	12.0 (7.85)	<0.0001				
Day 114	64	15.7 (5.20)	7.3 (6.34)	<0.0001				

BL = baseline; SD = standard deviation; LS = least squares; CI = confidence interval

a p-value calculated from paired-sample t-test at alpha = 0.05.

b p-value for the difference in the LS-means between the 2 groups.

c Patients could have received Venofer® and/or epoetin during the Extended Follow-Up Phase as needed to maintain a hemoglobin level between 11 and 12.5 g/dL, a TSAT of 25-50% and a ferritin level of 300-500 ng/mL.

Cross-reference: Appendix Tables 3.2.3.1, 3.2.3.2, and 3.2.3.3 and Appendix Listing 10.1

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 64

During the Extended Follow-Up Phase, statistically significant mean increases from baseline in TSAT values were observed at each visit. Mean changes from baseline across visits in TSAT values ranged from 4.5% to 12.0%.

Per Protocol Population

In the Per Protocol Population, analyses of mean changes from baseline in TSAT values were generally similar to those observed in the Intent-to-Treat Population, except that the change at Day 36 in the oral iron group was statistically significant. A statistically significant difference was observed between the treatment groups in the mean change from baseline to Day 43 in TSAT values ($p<0.001$), with a greater increase in TSAT values observed in the Venofer group (4.9%) compared to the oral iron group (0.9%).

Hemoglobin > 11.0 g/dL during the Study

Intent-to-Treat Population

During the Treatment Phase, a statistically significantly greater proportion of patients in the Venofer group (54.2%) attained hemoglobin values > 11.0 g/dL compared to the oral iron group (31.3%). During the Extended Follow-Up Phase, 74.4% of the patients attained hemoglobin values > 11.0 g/dL. At anytime during the Treatment or Extended Follow-Up Phases of the study, including both patients treated with oral iron or Venofer, 68.8% of the patients attained hemoglobin values > 11.0 g/dL. A summary of the proportions of patients who attained hemoglobin values > 11.0 g/dL during the Treatment and Extended Follow-Up Phases or at anytime during the study is presented in the table below.

Table 6.4f Proportions of Patients Who Attained Hemoglobin Values >11.0 g/dL During the Treatment and Extended Follow-Up Phases or at Anytime During the Study (Intent-to-Treat Population)

	Treatment Phase		
	Oral Iron	Venofer®	p-value[a]
Day 15	3/45 (6.7%)	7/47 (14.9%)	NC
Day 36	9/44 (20.5%)	10/41 (24.4%)	NC
Day 43	13/43 (30.2%)	22/39 (56.4%)	0.067
Anytime up to Day 43	15/48 (31.3%)	26/48 (54.2%)	0.028
	Extended Follow-Up Phase		
	Venofer®[b]		
Day 57	33/75 (44.0%)		
Day 71	41/72 (56.9%)		
Day 86	42/68 (61.8%)		
Day 100	41/65 (63.1%)		
Day 114	38/64 (59.4%)		
Anytime During Extended Follow-Up Phase	58/78 (74.4%)		
	During Study		
Anytime During Study	66/96 (68.8%)		

NC = Not calculated

a p-value using CMH test controlling by center.

b Patients could have received Venofer® and/or epoetin during the Extended Follow-Up Phase as needed to maintain a hemoglobin level between 11 and 12.5 g/dL, a TSAT of 25-50% and a ferritin level of 300-500 ng/mL.

Cross-reference: Appendix Table 3.2.4 and Appendix Listings 7.1 and 7.2

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 65

Reviewer's comments: The study showed that 30% of patients had their hemoglobin increased to 11 g/dL without increase in mean ferritin level in the oral iron group.

Per Protocol Population

In the Per Protocol Population, analyses of the proportions of patients who attained hemoglobin values > 11.0 g/dL were generally similar to those observed in the Intent-to-Treat Population, except that no statistically significant difference was noted for the analysis of anytime during the Treatment Phase.

Other Efficacy Analyses

Other efficacy analyses included the maximum level of hemoglobin during the Treatment and Extended Follow-Up Phases, the number of days to reach the maximum level of hemoglobin, the total iron required during the Extended Follow- Up Phase, and the change in epoetin dose from Day 1 to the end of the study.

Maximum Level of Hemoglobin

Intent-to-Treat Population

Among patients who completed the Treatment Phase, the mean maximum hemoglobin level was 10.7 g/dL in the oral iron group and 11.1 g/dL in the Venofer group. The mean number of days to reach the mean maximum hemoglobin level during the Treatment Phase was 33.1 days in the oral iron group and 36.4 days in the Venofer group.

Among patients who completed the Extended Follow-Up Phase, the mean maximum hemoglobin level was 11.8 g/dL. The mean number of days to reach the mean maximum hemoglobin level during the Extended Follow-Up Phase was 95.4 days.

A summary of the mean maximum hemoglobin levels and the number of days to reach the mean maximum hemoglobin levels during the Treatment and Extended Follow-Up Phases is presented in the table below.

Table 6.4g Maximum Hemoglobin Level and Number of Days to Attain Maximum Hemoglobin During the Treatment and Extended Follow-Up Phases (Intent-to-Treat Population)

	Treatment Phase	
	Oral Iron (N=48)	Venofer® (N=48)
Patients who completed Treatment Phase[a]	44	39
Maximum hemoglobin level		
Mean (SD)	10.7 (0.95)	11.1 (1.24)
95% CI	10.4, 11.0	10.7, 11.6
Median	10.7	11.3
Range	8.4 - 13.7	8.6 - 15.6
Days to reach maximum hemoglobin level[b]		
Mean (SD)	33.1 (11.82)	36.4 (9.91)
95% CI	29.5, 36.7	33.2, 39.6
Median	36.0	42.0
Range	12.0 - 46.0	13.0 - 48.0
	Extended Follow-Up Phase	
	Venofer®[c] (N=78)	
Patients who completed Extended Follow-Up Phase[a]	65	
Maximum hemoglobin level		
Mean (SD)	11.8 (1.02)	
95% CI	11.6, 12.1	
Median	11.8	
Range	9.7 - 14.5	
Days to reach maximum hemoglobin level[b]		
Mean (SD)	95.4 (16.60)	
95% CI	91.3, 99.5	
Median	99.0	
Range	57.0 - 121.0	

SD = standard deviation; CI = confidence interval

a Patients who did not complete the Phase were excluded from the summary.

b Days to reach maximum hemoglobin level was calculated by subtracting the earliest date patient achieved the maximum hemoglobin value from the first date of study drug +1.

c Patients could have received Venofer® and/or epoetin during the Extended Follow-Up Phase as needed to maintain a hemoglobin level between 11 and 12.5 g/dL, a TSAT of 25-50% and a ferritin level of 300-500 ng/mL.

Cross-reference: Appendix Table 3.3.1 and Appendix Listings 7.1 and 7.2

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 67

Per Protocol Population
In the Per Protocol Population, analyses of mean maximum hemoglobin levels and days to reach the mean maximum hemoglobin levels were similar to those observed in the Intent-to-Treat Population.

Iron Requirement during Extended Follow-Up Phase
In the Intent-to-Treat Population, only 1 (1.3%) patient did not require Venofer during the Extended Follow-Up Phase using pre-specified algorithm based on TSAT and ferritin values in the protocol. The majority of the patients (60.3%) required at least 5 doses of Venofer during the Extended Follow-Up Phase. The mean number of days from Day 29 during the Treatment Phase until the first dose of iron was required in the Extended Follow-Up Phase was 20 days. In the Per Protocol Population, analyses of iron requirements during the Extended Follow-Up Phase were similar to those observed in the Intent-to-Treat Population.

Epoetin Weekly Dose and Change in Weekly Dose
In the Intent-to-Treat Population, during the Treatment Phase, no statistically significant changes from baseline in mean epoetin dose were noted in either treatment group. Statistically significant mean increases from baseline in epoetin dose were observed at each visit during the Extended Follow-Up Phase except for the Day 71 and Day 79 visits. Mean changes from baseline across visits in epoetin dose ranged from 92.9 U to 309.0 U. In the Per Protocol Population, analyses of mean change from baseline to each visit in epoetin dose during the Treatment and Extended Follow-Up Phases were similar to those observed in the Intent-to-Treat Population.

Quality of Life
Quality of life was measured using normalized SF-36 data using only the Intent-to-Treat Population. No statistically significant differences were observed between the treatment groups for the mean change from baseline to Day 43 in the health concept categories of physical functioning, role-physical, bodily pain, general health, vitality, social functioning, and mental health. A statistically significant difference was observed between the treatment groups for the mean change from baseline to Day 43 in the health concept category of role-emotional, with a greater mean increase noted in the Venofer group compared with the oral iron group.

In the mean change from baseline to Day 114 in the health concept categories, the only statistically significant increase noted was for role-emotional.

At the Day 43 visit, 45.4% of the patients in the Venofer group and 36.4% of the oral iron group reported feeling much or somewhat better compared to 1 year ago. At the Day 114 visit, 61.7% of the patients reported feeling much or somewhat better compared to 1 year ago.

Supplemental Analyses

In an effort to determine meaningful changes in hemoglobin and iron indices, analyses were performed summarizing the proportions of patients who demonstrated a hemoglobin change $\geq$0.8 g/dL, a ferritin change $\geq$ 160 ng/mL, a TSAT change $\geq$ 5%, and the proportions of patients who

met the change in hemoglobin/TSAT criteria, the hemoglobin/ferritin/TSAT criteria, and the ferritin/TSAT criteria.

By Day 43 of the Treatment Phase, a change in hemoglobin of ≥ 0.8 g/dL was achieved by 33 (68.8%) of the Venofer patients and by 23 (47.9%) of the oral iron patients, a change in ferritin of ≥ 160 ng/mL was achieved by 42 (87.5%) of the Venofer patients and none of the oral iron patients, and a change in TSAT of $\geq 5\%$ was achieved by 28 (58.3%) of the Venofer patients and by 18 (37.5%) of the oral iron patients. The proportions of Venofer patients who met the hemoglobin/TSAT criteria (47.9%), the hemoglobin/ferritin/TSAT (43.8%), and the ferritin/TSAT criteria (54.2%) were statistically significantly higher than those observed among oral iron patients (22.9%, 0%, and 0%, respectively). The primary result of these analyses indicate that the majority of the Venofer patients exhibited increases in ferritin ≥ 160 ng/mL, while none of the oral iron patients achieved this criterion.

A summary of the proportions of patients who achieved specified laboratory criteria during the Treatment Phase is presented in the table below.

Table 6.4h Summary of Proportions of Patients Who Achieved Specified Laboratory Criteria by Day 43 of the Treatment Phase (Intent-to-Treat Population)

By Day 43	Oral Iron (N=48)	Venofer® (N=48)	p-value
Hemoglobin Change (≥0.8 g/dL)	23 (47.9%)	33 (68.8%)	0.0618
Ferritin Change (≥160 ng/mL)	0	42 (87.5%)	0.000
TSAT Change (≥5%)	18 (37.5%)	28 (58.3%)	0.0654
Hemoglobin Change/TSAT Change	11 (22.9%)	23 (47.9%)	0.0183
Hemoglobin Change/Ferritin Change/TSAT Change	0	21 (43.8%)	0.000
Ferritin Change/TSAT Change	0	26 (54.2%)	0.000

Cross-reference: Appendix Tables 3.2.1.3b and Appendix Listing 7.1

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 69

Use of an Efficacy Subset of Patients

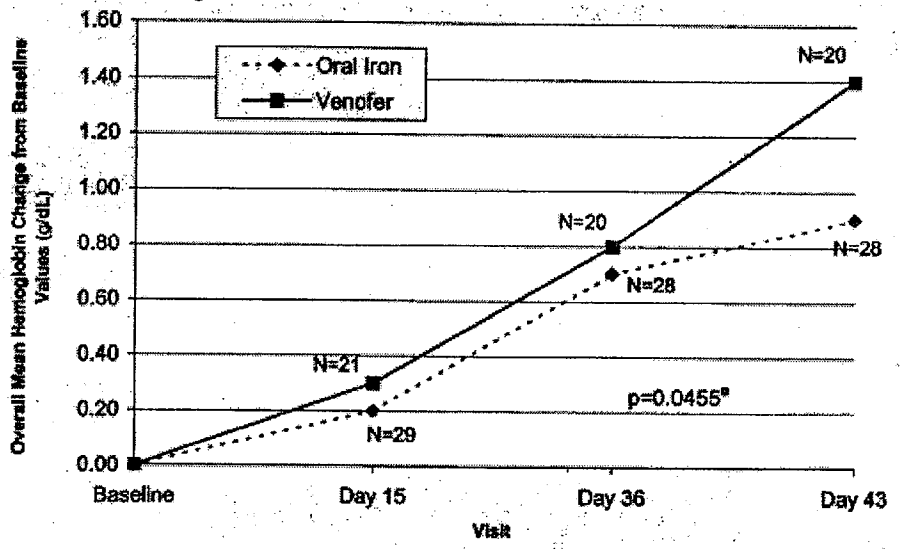
Examination of change from baseline to Day 43 in hemoglobin, ferritin, hematocrit, and TSAT and the proportions of patients who achieved clinical success with regard to several covariates was done. Covariates considered included baseline ferritin < 100 ng/mL, epoetin usage, age group (≥ 65 or < 65), gender, race (Caucasian, Black and other), and study center. Results are presented only for the Intent-to-Treat Population.

Baseline Ferritin < 100 ng/mL

Among patients with a baseline ferritin < 100 ng/mL, which indicates iron-depleted patients, statistically significant differences were observed between the treatment groups in the mean change from baseline to Day 43 in hemoglobin, ferritin, hematocrit, and TSAT values, with greater mean increases noted in the Venofer group compared to the oral iron group.

Venofer patients with a baseline ferritin < 100 ng/ mL had a statistically significant greater increase in hemoglobin at Day 43 (1.4 g/dL) compared to the oral iron group (0.9 g/dL). Mean

changes from baseline in hemoglobin values for patients with baseline ferritin < 100 ng/mL are presented in the figure below.



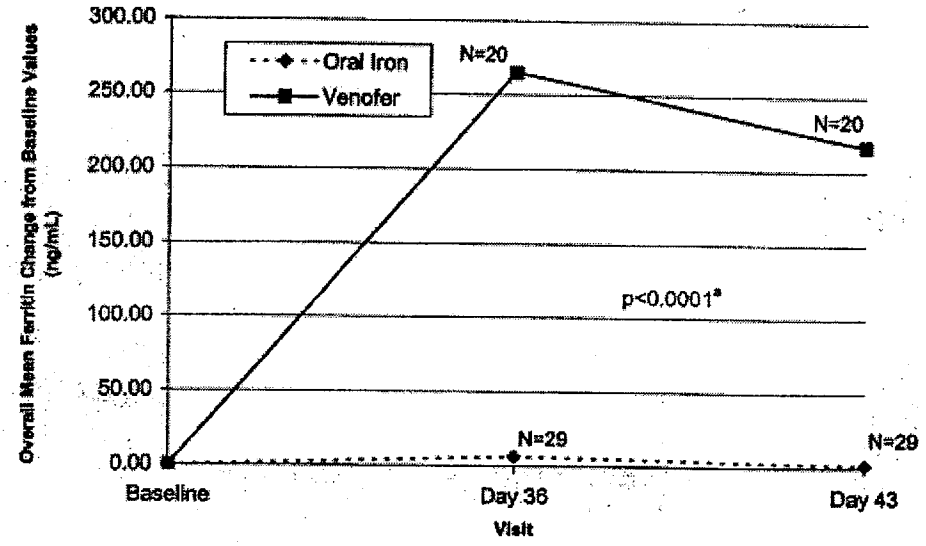
a p-value calculated from LS means.
Cross-Reference: Appendix Tables 3.4.1.1 and 3.4.1.2

Figure 6.4d Mean Changes From Baseline in Hemoglobin Values for Patients With Baseline Ferritin <100 ng/mL (Intent-to-Treat Population)

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 72

Venofer patients with a baseline ferritin < 100 ng/mL had a statistically significant greater increase in ferritin at Day 43 (217.0 ng/mL) compared to the oral iron group (1.6 ng/mL).

Mean changes from baseline in ferritin values for patients with baseline ferritin < 100 ng/mL are presented in Figure below.



a p-value calculated from LS means.
Cross-Reference: Appendix Tables 3.4.2.1 and 3.4.2.2

Figure 6.4e Mean Changes From Baseline in Ferritin Values for Patients With Baseline Ferritin <100 ng/mL (Intent-to-Treat Population)

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 73

Increases in hematocrit (4.6%) and TSAT (5.9%) were also statistically significantly higher in Venofer patients with a baseline ferritin level < 100 ng/mL compared with oral iron patients (3.1 % and 1.3%, respectively).

A summary of the mean changes from baseline to Day 43 in hemoglobin, ferritin, hematocrit, and TSAT values for patients with baseline ferritin levels < 100 ng/mL is presented in the table below.

Table 6.4i Summary of Mean Changes From Baseline to Day 43 in Hemoglobin (g/dL), Ferritin (ng/mL), Hematocrit (%), and TSAT (%) During the Treatment Phase (Patients with Baseline Ferritin <100 ng/mL)

	Treatment Phase							
	Oral Iron (N=31)				Venofer® (N=21)			
	N	BL (SD)	Change from BL (SD)	p-value[a]	N	BL (SD)	Change from BL (SD)	p-value[a]
Hemoglobin	28	9.7 (0.75)	0.9 (1.02)	<0.0001	20	9.8 (0.67)	1.4 (0.62)	<0.0001
LS Means 95% CI	0.87 0.54, 1.21				1.40 1.01, 1.80			
	Venofer® - Oral Iron LS Mean: 0.53 95% CI: 0.01, 1.05							
p-value[b]	p=0.0455							
Ferritin	29	55.9 (24.57)	1.6 (34.42)	0.800	20	52.8 (26.44)	217.0 (99.99)	<0.0001
LS Means 95% CI	5.55 -16.66, 27.77				219.61 192.39, 246.82			
	Venofer® - Oral Iron LS Mean: 214.05 95% CI: 178.62, 249.48							
p-value[b]	p<0.0001							
Hematocrit	28	30.4 (2.19)	3.1 (3.05)	<0.0001	20	31.2 (2.13)	4.6 (2.54)	<0.0001
LS Means 95% CI	3.05 2.02, 4.08				4.73 3.51, 5.94			
	Venofer® - Oral Iron LS Mean: 1.67 95% CI: 0.08, 3.27							
p-value[b]	p=0.0404							
TSAT	29	14.1 (5.56)	1.3 (6.07)	0.245	20	16.0 (5.77)	5.9 (7.93)	0.004
LS Means 95% CI	0.54 -1.61, 2.68				7.06 4.45, 9.67			
	Venofer® - Oral Iron LS Mean: 6.52 95% CI: 3.05, 10.00							
p-value[b]	p=0.0005							

BL = baseline; SD = standard deviation; LS = least squares; CI = confidence interval

a p-value calculated from paired-sample t-test at alpha = 0.05.

b p-value for the difference in the LS-means between the 2 groups.

Cross-reference: Appendix Tables 3.4.1.1, 3.4.1.2, 3.4.2.1, 3.4.2.2, 3.4.3.1, 3.4.3.2, 3.4.4.1, and 3.4.4.2 and Appendix Listing 10.1

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 74

Clinical success (defined as ≥ 0.8 g/dL change from baseline in hemoglobin and ≥160 ng/mL change from baseline in ferritin at any timepoint during the Treatment Phase) was achieved by 81.0% (17/ 21) of the Venofer patients and none of the oral iron patients who had a baseline ferritin < 100 ng/mL.

Reviewer's comments: The results showed clearly that iron depleted patients had the greater benefit from Venofer treatment than from oral iron treatment. Patients with chronic renal disease with iron deficiency should be an appropriate target population for the Venofer treatment.

Epoetin Usage

After adjusting for epoetin use, there was no statistically significant overall treatment effect between the groups in the mean change from baseline to Day 43 in hemoglobin and hematocrit. A statistically significant overall treatment effect was observed after adjusting for epoetin use in

the mean change from baseline to Day 43 in ferritin and TSAT, with greater mean increases noted in the Venofer group compared to the oral iron group.

Reviewer's comments: The result further suggested that the increase in hemoglobin was mainly due to the start of epoetin use in study patients.

Clinical success (defined as an increase of $\geq$ 0.8 g/dL from baseline in hemoglobin and an increase of $\geq$160 ng/mL change from baseline in ferritin at any timepoint during the Treatment Phase) was achieved by 60.0% (24/40) of the Venofer patients who were epoetin naive and 75.0% (6/8) of the Venofer patients who were epoetin users. None of the oral iron patients achieved clinical success by the sponsor's definition.

D. Efficacy Conclusions

One study (1VEN99012) was submitted to support the indication for treatment of iron deficiency anemia in chronic kidney disease patients not on dialysis.

Study 1VEN 99012 was a multicenter, randomized, open-label, parallel groups study of Venofer 200 mg IV weekly for 5 doses as compared to oral iron (ferrous sulfate) 325 mg three times a day for 29 days in patients with chronic kidney disease not on dialysis. Patients with creatinine clearance < 40 ml/min, hemoglobin < 10.5 g/dL, TSAT < 25% and serum ferritin < 300 ng/mL were enrolled in the study. The primary efficacy endpoints of the study were the mean changes at Day 43 from baseline in hemoglobin and ferritin levels. The differences in the mean change in hemoglobin and ferritin from baseline between the two treatment groups were tested (each was to be tested at α=0.025).

A total of 102 patients (53 patients in the Venofer group and 49 patients in the oral iron group) were randomized, 96 patients (48 patients in each group) were treated, and 82 patients (39 patients in the Venofer group and 43 patients in the oral iron group) were evaluated for primary efficacy endpoints in the study. Patients ranged in age from 27 to 91 years (mean ages of 62 years in the Venofer group and 60 year in the oral iron group) with more than 60% of females (60% in the Venofer group and 71% in the oral iron group). Patients were Caucasian (38% in the Venofer group and 44% in the oral iron group), Hispanic (35% in the Venofer group and 23% in the oral iron group), Black (23% in the Venofer group and 29% in the oral iron group), and Asian (4% in each group). The majority of patients were epoetin naïve (83% in the Venofer group and 90% in the oral iron group).

The study failed to demonstrate that Venofer is superior to oral iron in increasing hemoglobin at Day 43 from baseline in patients with chronic kidney disease not on dialysis (1.0 mg/dL in the Venofer group and 0.7 mg/dL in the oral iron group, p=0.14). The study showed a significant difference in an increase in ferritin level at Day 43 from baseline between the Venofer group and the oral iron group (288 ng/mL and -5.1 ng/mL, respectively, p<0.0001). However, change in hemoglobin is a more clinically relevant and important endpoint than change in ferritin for

treatment of anemia in patients with chronic kidney disease not on dialysis since the main cause of anemia may not be iron deficiency in these patients.

The study showed significant increases in hemoglobin at Day 43 as compared to baseline in both treatment groups ($p<0.02$ in the Venofer group and $p<0.002$ in the oral iron group). Since the majority of patients were epoetin naïve and initiated epoetin treatment at the same time iron therapy was initiated in the study, an increase in hemoglobin from baseline may be due (at least in part) to new use of epoetin therapy in the both treatment groups. This was supported by an increase of hemoglobin (0.7 mg/dL) without an increase of ferritin level (-5.1 ng/mL) in the oral iron group. In a subgroup analysis, in patients with ferritin <100 ng/mL at baseline (20 in the Venofer group and 29 in the oral iron group) there was greater increase in hemoglobin from baseline in the Venofer group as compared to the oral iron group (1.4 g/dL and 0.9 g/dL, respectively, $p=0.046$).

The secondary efficacy analyses had similar findings. The results showed no significant difference in an increase in hematocrit at Day 43 from baseline between the Venofer group and the oral iron group (3.7% and 2.8%, respectively, $p=0.12$). There was a significant difference in an increase in TSAT at Day 43 from baseline between the Venofer group and the oral iron group (4.5% and 0.5%, respectively, $p<0.0001$).

It is noteworthy that a significant proportion of randomized patients were not included in the primary efficacy analysis [26 % (14/53) in the Venofer group and 12% (6/49) in the oral iron group)]. There were 9% of patients who discontinued study before the treatment and 17% of patients who did not complete the treatment in the Venofer group as compared to 2% and 10%, respectively, in the oral iron group. These may affect the efficacy and safety results of the study.

There was a notable imbalance in the iron status at baseline between the two treatment groups. Patients with TSAT <20% and ferritin <100 ng/mL were 33% in the Venofer group and 54% in the oral iron group. Also, there was an uneven distribution in age, gender and race between the two treatment groups.

Overall, the results from Study 1VEN99012 do not provide adequate support for the proposed indication for the treatment of iron deficiency anemia in patients with chronic kidney disease not on dialysis. An adequate and well-controlled study to demonstrate the effectiveness of Venofer in terms of an increase in hemoglobin in iron deficiency patients with chronic kidney disease not on dialysis will be needed. The study should be a randomized, parallel groups, controlled study. The study patients should be patients who have received epoetin therapy with a stable dose for at least 3 months before the study and who will maintain the previous epoetin dose as much as possible during the study.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Only one study (Study 1VEN99012) was conducted in CKD patients not on dialysis by the sponsor. In this study, 48 patients were exposed to Venofer 200 mg by slow injection over 5 minutes for about 5 doses during the treatment phase and 78 patients were exposed to Venofer 200 mg for about 5 doses during the extended phase of the study. A total of 91 patients with CKD not on dialysis were exposed to Venofer 200 mg doses administered over 5 minutes in the study.

The overall incidences of treatment-emergent adverse events were similar between the Venofer group (87.5%, 42/48) and the oral iron group (89.6%,43/48) during the treatment phase. However, patients in the Venofer group experienced more cardiovascular, endocrine, general and administration site, nervous system, and vascular disorders than in the oral iron group while patients in the oral iron group experienced more gastrointestinal (except for taste disturbance and diarrhea) and skin and subcutaneous tissue disorders than in the Venofer group. Gastrointestinal disorders were the most commonly experienced treatment-emergent adverse events in both treatment groups (47.9% in the oral iron group and 35.4% in the Venofer group). AEs that occurred more frequently with Venofer treatment than with oral iron treatment included edema (8.3% vs. 2.1%), hyperglycemia (8.3% vs. 0%), taste disturbance (8.3% vs. 0%), dizziness (8.3% vs. 2.1%), hypertension aggravated (8.3% vs. 2.1%), and injection site burning (6.3% vs. 0%). AEs occurred more frequently with oral iron treatment than with Venofer treatment included nausea (16.7% vs. 12.5%) vomiting (12.5% vs. 8.3%), constipation (14.6% vs. 2.1%), pruritus (12.5% vs. 2.1%), abdominal pain (6.3% vs. 2.1%), weakness (6.3% vs. 0%), and nasal congestion (6.3% vs. 2.1%).

During the Extended Follow-Up Phase, at least one treatment-emergent adverse event was experienced by 78.2% (61/78) of the patients. The most commonly experienced treatment-emergent adverse events were diarrhea (12.8%), vomiting (9.0%), edema lower limb (9.0%), and arthralgia (9.0%).

During the whole study period, patients experienced more adverse events including cardiovascular disorders, diarrhea, taste disturbance, muscular pain, headache, dizziness, and hypertension with Venofer treatment than with oral iron treatment. Patients experienced more nausea and vomiting with oral iron treatment than with Venofer treatment.

More gastrointestinal disorders including constipation, nausea, and abdominal pain were attributed to oral iron treatment by the investigators. Taste disturbance, injection site reactions, limb pain, headache, dizziness, and pruritis were attributed to Venofer treatment by the investigators.

One patient died at 5 days after the last Venofer dose during the Extended Follow-Up Phase. The patient was a 74-year-old male with significant cardiac history who received Venofer 200 mg during the Treatment Phase and 2 additional Venofer doses in the extended follow-up. The patient experienced 2 non-serious adverse events during the Treatment Phase (+2 edema on Day 8 and stiff neck on Day 35) that were considered by the Investigator to be not related to study medication. The cause of death was attributed to cardiopulmonary arrest secondary to coronary artery disease and hypertension and was considered unrelated to Venofer by the investigator.

None of patients in the oral iron group died during the study and within 30 days after receiving study drug.

During the Treatment Phase, 7 (14.6%) patients in the Venofer group and 2 (4.2%) patients in the oral iron group experienced at least 1 serious adverse event. More patients experienced more SAEs including congestive heart failure, pulmonary edema, fluid overload, hyperglycemia, renal failure, and benign intracranial hypertension with Venofer treatment than with oral iron treatment. None of these serious adverse events was considered by the investigator to be related to study medication.

More patients discontinued the treatment prematurely due to AEs in the Venofer group (12.5%) than in the oral iron group (2.1%) during the treatment phase. An additional 10% of patients who were enrolled in the extended treatment phase prematurely discontinued the treatment due to adverse events.

No cases of hypersensitivity/allergic reaction were reported with Venofer treatment in the study. One case of hypotension was reported with oral iron treatment. No case of hypotension was reported during the treatment phase and 4 (5%) cases of hypotension were reported during the Extended Follow-Up Phase. None of these events was considered related to study drug by the investigators.

Only 3 published papers on studies in patients with CKD not on dialysis were found in a search of the literature. Safety information from these studies was limited.

Most adverse events reported by post-marketing spontaneous reports have been included in the current labeling.

In conclusion, there is limited safety information for Venofer in CKD patients not on dialysis. Clinical study 1VEN99012 showed that patients experienced more adverse events (except for gastrointestinal disorders), serious adverse events, and premature discontinuation due to adverse events with Venofer treatment than with oral iron treatment.

B. Description of Patient Exposure

A total of 48 patients with CKD not on dialysis were exposed to Venofer 200 mg during the treatment phase. A summary of the extent of exposure during the Treatment Phase of the study is presented in the table below.

Table 6.6a Summary of Extent of Exposure During the Treatment Phase (Safety Evaluable Population)

Total Dose of Iron (mg) Received	Oral Iron[a] (N=48)	Venofer® (N=48)
Mean (SD)	4835.7 (1241.12)	950.4 (156.18)
95% Confidence Interval of Mean	4484.6, 5186.8	906.2, 994.6
Median	5265.0	1000.0
Minimum - Maximum	65.0 - 5655.0	200.0 - 1000.0

SD=Standard Deviation

a Patient 04-065 received only 1 dose of oral iron.

Cross-reference: Appendix Table 5.1 and Appendix Listing 8.1

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 78

During the Treatment Phase, the mean milligram (±SD) exposure, calculated as the total dose of study drug administered, was 4835.7 (±1241.12) mg in the oral iron group and 950.4 (±156.18) (about 5 doses) in the Venofer group.

During the Extended Follow-Up Phase, a total of 78 patients were exposed to Venofer 200 mg including 35 patients who received Venofer 200 mg during treatment phase and 43 patients who received oral iron during the treatment phase. The mean milligram (±SD) exposure in these patients, calculated as the total dose of Venofer administered, was 970.5 ± 472.93 mg (about 5 doses).

A total of 91 patients were exposed to Venofer 200 mg either in treatment or extended follow-up phases.

C. Methods and Specific Findings of Safety Review

Overview of Clinical Studies

One study (1VEN99012) was conducted by the sponsor to compare the efficacy and safety of Venofer 200 mg administered as an intravenous injection plus epoetin to oral iron plus epoetin in CRF patients not receiving dialysis. The sponsor also included summaries of three other studies of Venofer in the CKD patient population not receiving dialysis reported in the literature.

The sponsor's following table summarizes Study 1VEN99012 and the 3 studies reported in the literature.

Table 8.6a Studies of Venofer® Included in the Integrated Summary of Safety

Ref. Vol. Pages	Study - Investigator - Coordinating Center(s) - Publication Ref.	Design	Number of Subjects, Sex, and Age	Diagnosis and Criteria for Inclusion	Duration of Treatment	Test Product Dosage Regimen Route of Administration	Reference Therapy Dose Regimen Route of Administration	Criteria for Evaluation
Protocol # 1VEN99012: CRF Patients Not Receiving Dialysis								
Volume 31 Page 1	Charytan C, Qunibi W, Singh H, Schwenk M, Aronoff G, Besarab A. Safety of Venofer®, [Iron Sucrose Injection, U.S. P.] administered by rapid IV push (IVP) in predialysis CKD patients. *J Am Soc Nephro* 2002;13:521a.	Randomized, open-label, multicenter, active-controlled study	Oral Iron: 48 patients 14 Males & 34 Females Mean Age: 60±14.0 yrs. Venofer® 48 patients 19 Males & 29 Females Mean Age: 62±14.4 yrs.	CRF patients >18 years of age, not yet on dialysis, with a creatinine clearance <40 mL/min, Hgb <10.5 g/dL based on the average of 2 qualifying values drawn on different days, TSAT <25%, and serum ferritin <300 ng/mL.	5 months	Treatment Phase Venofer® 200 mg IV injection on Days 1, 8, 15, 22, and 29. All patients received epoetin 2000 U SC weekly through Day 43. Extended Follow-Up Patients who required iron (including those in the oral iron group) received Venofer® and/or epoetin as needed to maintain Hgb between 11-12.5 g/dL, TSAT of 25-50%, and a ferritin of 300-500 ng/mL.	Treatment Phase Ferrous Sulfate 325 mg TID orally on Days 1-29 All patients received epoetin 2000 U SC weekly through Day 43.	Primary Efficacy: Change from BL to Day 43 in Hgb and serum ferritin. Secondary: change from BL to Day 43 in Hct, TSAT, the number of patients who attained Hgb >11 g/dL, the change from BL in epoetin and iron requirements, and change from BL in QOL. Additional: # of patients who achieved clinical success, defined as a change in Hgb ≥0.8 g/dL and a change in serum ferritin ≥160 ng/mL from BL up to Day 43 and maximum level of Hgb Safety: Adverse events, labs, ECGs, vital signs, and PEs

DOQI = Disease Outcomes Quality Initiative; CKD = Chronic Kidney Disease; CRF = Chronic Renal Failure; HDAA = hemodialysis associated anemia; Hgb = hemoglobin; TSAT = serum transferrin saturation; IV = intravenous; HD = hemodialysis; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; SC = subcutaneously; TIBC = total iron-binding capacity; TID = three times daily; EPO = erythropoietin; BL = baseline; Hct = hematocrit; PE = physical examination; ECG = electrocardiogram

Table 8.6a Studies of Venofer® Included in the Integrated Summary of Safety (Continued)

Ref. Vol. Pages	Study - Investigator - Coordinating Center(s) - Publication Ref.	Design	Number of Subjects, Sex, and Age	Diagnosis and Criteria for Inclusion	Duration of Treatment	Test Product Dosage Regimen Route of Administration	Reference Therapy Dose Regimen Route of Administration	Criteria for Evaluation
Published Literature: CRF Patients Not Receiving Dialysis								
Volume 31 Page 77	Stoves J, Inglis H, Newstead CG, Dept of Nephrol. St. James's University Hosp. Leeds, UK. *Nephrol Dial Transplant* 2001;16:967-74.	Randomized prospective study	45 patients. Oral Iron Group: 23 patients [15 Males & 8 Females]; Mean Age: 59.9±13.4 yrs. IV Iron Group: 22 patients [10 Males & 12 Females] Mean Age: 57.3±14.0 yrs.	Patients with progressive renal insufficiency and worsening anemia defined as Hgb <11 g/dL.	6 months	Venofer®: 300 mg over 2 hours, repeated monthly Epoetin at an initial dose of 2000 U twice weekly.	Oral Iron [ferrous sulfate]: 200 mg TID. Epoetin at an initial dose of 2000 U twice weekly.	Hgb, hypochromic red blood cells, serum ferritin, creatinine, parathormone and c-reactive protein were monitored monthly.
Volume 31 Page 85	Silverberg DS, Blum M, Agbaria Z, *et al.* Nephrol. & Hematol. Tel Aviv Med. Center, Tel Aviv, Israel *Clin Neph* 2001;55(3):212-9.	Randomized prospective study	90 predialysis patients. Group A [IV Iron & EPO] 25 Males & 20 Females Mean Age: 68.05±11.95 yrs. Group B [IV Iron only] 25 Males & 20 Females; Mean Age: 69.22±12.81 yrs.	Patients with CRF with creatinine clearances of 10-40 mL/min/1.73 m^2, aged 25-80 and with a Hct of <35%.	5 weeks	Venofer® Group A: 200 mg of elemental iron as Venofer® was given IV in 150 mL of normal saline over 60 minutes. This dose was given weekly for 5 doses. The patients also received 2000 IU of EPO weekly for 5 doses. Group B: Same iron dose, but no EPO.	None	Hematologic and biochemical parameters were monitored at baseline and at the end of the 5-week study. Some patients were followed for an additional 12 months.

DOQI = Disease Outcomes Quality Initiative; CKD = Chronic Kidney Disease; CRF = Chronic Renal Failure; HDAA = hemodialysis associated anemia; Hgb = hemoglobin; TSAT = serum transferrin saturation; IV = intravenous; HD = hemodialysis; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; SC = subcutaneously; TIBC = total iron-binding capacity; TID = three times daily; EPO = erythropoietin; BL = baseline; Hct = hematocrit; PE = physical examination; ECG = electrocardiogram

Table 8.6a Studies of Venofer® Included in the Integrated Summary of Safety (Continued)

Ref. Vol. Pages	Study - Investigator - Coordinating Center(s) - Publication Ref.	Design	Number of Subjects, Sex, and Age	Diagnosis and Criteria for Inclusion	Duration of Treatment	Test Product Dosage Regimen Route of Administration	Reference Therapy Dose Regimen Route of Administration	Criteria for Evaluation
Published Literature: CRF Patients Not Receiving Dialysis								
Volume 31 Page 100	Silverberg DS, Iaina A, Peer G, *et al.* Dept of Nephrol. Ichilov Hospital., Tel Aviv, Israel *Am J Kid Dis* 1996;27(2):234-8.	Open-label prospective study	33 predialysis patients. 18 Males & 15 Females 27 to 74 years of age.	Patients with CRF with creatinine clearances of 10-40 mL/min, with a Hgb of <11.0 g/dL.	5 months	200 mg of elemental iron as Veno-Ferrum was given IV in 150 mL of normal saline over 2 hours. This dose was given once monthly for 5 months. All patients also received a slow-release oral preparation (100 mg elemental iron per day).	None	Hgb, Hct, serum ferritin, iron, TIBC, and TSAT were monitored at 3 and 6 months. Safety: adverse events

DOQI = Disease Outcomes Quality Initiative; CKD = Chronic Kidney Disease; CRF = Chronic Renal Failure; HDAA = hemodialysis associated anemia; Hgb = hemoglobin; TSAT = serum transferrin saturation; IV = intravenous; HD = hemodialysis; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; SC = subcutaneously; TIBC = total iron-binding capacity; TID = three times daily; EPO = erythropoietin; BL = baseline; Hct = hematocrit; PE = physical examination; ECG = electrocardiogram

Sponsor's table in NDA/SE1-008 submission Vol. 16, pp. 3-5

Study 1VEN99012

Adverse Events

During Treatment Phase

Treatment-emergent adverse events:

During the Treatment Phase, at least one treatment-emergent adverse event was experienced by 87.5% (42/48) of the patients in the Venofer group and 89.6% (43/48) of the patients in the oral iron group. The most commonly experienced treatment-emergent adverse events in the oral iron group were nausea (16.7%), constipation (14.6%), vomiting (12.5%), pruritus (12.5%), and diarrhea (10.4%). The most commonly experienced treatment-emergent adverse events in the Venofer group were nausea (12.5%) and diarrhea (10.4%). A summary of treatment-emergent adverse events experienced by 3 or more patients in either treatment group during the Treatment Phase is presented in the table below.

Table 6.6b Treatment-Emergent Adverse Events Experienced by 3 or More Patients in Either Treatment Group During the Treatment Phase (Safety Evaluable Population)

MedDRA SOC Preferred Term	Oral Iron (N=48)	Venofer® (N=48)
At Least One Treatment-Emergent Adverse Event	43 (89.6%)	42 (87.5%)
Cardiac Disorders	8 (16.7%)	12 (25.0%)
Edema NOS	1 (2.1%)	4 (8.3%)
Endocrine Disorders	3 (6.3%)	7 (14.6%)
Hyperglycemia NOS	0	4 (8.3%)
Gastrointestinal Disorders	23 (47.9%)	17 (35.4%)
Nausea	8 (16.7%)	6 (12.5%)
Diarrhea NOS	5 (10.4%)	5 (10.4%)
Vomiting NOS	6 (12.5%)	4 (8.3%)
Taste Disturbance	0	4 (8.3%)
Abdominal Pain NOS	3 (6.3%)	2 (4.2%)
Constipation	7 (14.6%)	1 (2.1%)
General Disorders and Administration Site Conditions	5 (10.4%)	9 (18.8%)
Injection Site Burning	0	3 (6.3%)
Weakness	3 (6.3%)	0
Nervous System Disorders	5 (10.4%)	9 (18.8%)
Dizziness (exc. Vertigo)	1 (2.1%)	4 (8.3%)
Respiratory, Thoracic, and Mediastinal Disorders	9 (18.8%)	9 (18.8%)
Nasal Congestion	3 (6.3%)	1 (2.1%)
Skin and Subcutaneous Tissue Disorders	12 (25.0%)	6 (12.5%)
Pruritus NOS	6 (12.5%)	1 (2.1%)
Vascular Disorders	5 (10.4%)	7 (14.6%)
Hypertension Aggravated	1 (2.1%)	4 (8.3%)

NOS=not otherwise specified.
Cross-reference: Appendix Table 6.3.1 and Appendix Listing 9.1.1
Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 80

The majority of the treatment-emergent adverse events experienced during the Treatment Phase of the study were considered by the investigator to be mild or moderate in intensity. Severe

treatment-emergent adverse events were experienced by 1 patient (2.1%) in the oral iron group and 4 patients (8.3%) in the Venofer group. The severe treatment-emergent adverse events included one report each of congestive cardiac failure, fluid overload, pulmonary edema, diabetic ketoacidosis, pneumonia, muscle cramps, hypovolemia, benign intracranial hypertension, and headache. None of these 9 severe events was considered by the investigator to be study drug-related.

A greater number patients in the Venofer group experienced treatment-emergent taste disturbance (8.3%; 4/48) as compared to that in the oral iron group (0%; 0/48). Taste disturbance was characterized as "maple syrup taste" (2 patients), "metallic taste" (1 patient), or "funny taste in mouth" (1 patient) during study drug infusion; each of the taste disturbance events was considered related to Venofer. Additionally, treatment-emergent injection site burning was experienced by 6.3% of the patients in the Venofer group; each of the injection site burning events was considered related to Venofer. Treatment-emergent adverse events experienced by more patients in the Venofer group compared with the oral iron group included edema (8.3% versus 2.1%), hyperglycemia (8.3% versus 0%), dizziness (8.3% versus 2.1%), and hypertension aggravated (8.3% versus 2.1%); most of these events were considered unrelated to study drug by the investigators.

Treatment-emergent adverse events experienced by more patients in the oral iron group compared with the Venofer group included constipation (14.6% versus 2.1%, respectively) and pruritus (12.5% versus 2.1%, respectively). In the oral iron group, none of the pruritus events was considered drug-related; however, all of the constipation events were considered drug-related. In the Venofer group, the 1 pruritus event was considered drug-related and the 1 constipation event was considered unrelated to study drug.

Reviewer's comments: Patients in the Venofer group experienced more cardiovascular, endocrine, general and administration site, nervous system, and vascular disorders than did patients in the oral iron group. Patients in the oral iron group experienced more gastrointestinal (except for taste disturbance and diarrhea) and skin and subcutaneous tissue disorders than did patients in the Venofer group.

Drug-related treatment-emergent adverse events considered by investigators:

During the Treatment Phase, at least one drug-related treatment-emergent adverse event was experienced by 39.6% (19/48) of the patients in the oral iron group and 22.9% (11/48) of the patients in the Venofer group. The most commonly experienced drug-related treatment-emergent adverse events in the oral iron group were constipation (14.6%), nausea (10.4%), vomiting (8.3%), and diarrhea (6.3%). The most commonly experienced drug-related treatment-emergent adverse events in the Venofer group were taste disturbance (8.3%), and injection site burning (6.3%). A summary of drug-related treatment-emergent adverse events experienced by 3 or more patients in either treatment group during the Treatment Phase is presented in the table below.

Table 8.6d Drug-Related Treatment-Emergent Adverse Events Experienced by 3 or More Patients in Either Treatment Group During the Treatment Phase (Safety Evaluable Population; Study 1VEN99012)

MedDRA SOC Preferred Term	Oral Iron (N=48)	Venofer® (N=48)
At Least One Drug-Related Treatment-Emergent Adverse Event	**19 (39.6%)**	**11 (22.9%)**
Gastrointestinal Disorders	17 (35.4%)	6 (12.5%)
Taste Disturbance	0	4 (8.3%)
Nausea	5 (10.4%)	2 (4.2%)
Constipation	7 (14.6%)	0
Vomiting NOS	4 (8.3%)	0
Diarrhea NOS	3 (6.3%)	0
General Disorders and Administration Site Conditions	1 (2.1%)	4 (8.3%)
Injection Site Burning	0	3 (6.3%)

NOS=not otherwise specified.

Cross-reference: Appendix Table 6.3.3 and Appendix Listing 9.1.1

Sponsor's table in NDA/SE1-008 submission Vol. 16, pp. 14

The most notable difference between the oral iron and Venofer groups during the Treatment Phase of the study was for the overall incidence of drug-related gastrointestinal disorders. Greater numbers of patients in the oral iron group reported drug-related gastrointestinal disorders (35.4%) compared to the Venofer group (12.5%). The difference in drug-related gastrointestinal disorders was primarily the result of the increased incidence of constipation among patients in the oral iron group compared to the Venofer group. Additionally, nausea, vomiting, and diarrhea were each experienced by more patients in the oral iron group compared with the Venofer group.

During the Treatment Phase, patients in the oral iron group experienced treatment-emergent adverse events of hypoglycemia (2.1%), dermatitis (2.1%), hypertension aggravated (2.1%), and hypotension (2.1%) that were all considered by the investigator to be related to epoetin administration. Patients in the Venofer group experienced treatment-emergent adverse events of short-term memory loss (2.1%), blood pressure fluctuation (2.1%), and hypertension aggravated (2.1%) that were all considered by the investigator to be related to epoetin administration.

During Extended Follow-Up Phase

During the Extended Follow-Up Phase, at least one treatment-emergent adverse event was experienced by 78.2% (61/78) of the patients. The most commonly experienced treatment-emergent adverse events were diarrhea (12.8%), vomiting (9.0%), edema of lower limb (9.0%), and arthralgia (9.0%). A summary of treatment-emergent adverse events experienced by 3 or more patients during the Extended Follow-Up Phase is presented in the table below.

Table 6.6d Treatment-Emergent Adverse Events Experienced by 3 or More Patients During the Extended Follow-Up Phase (Safety Evaluable Population)

MedDRA SOC Preferred Term	Venofer®[a] (N=78)
At Least One Treatment-Emergent Adverse Event	**61 (78.2%)**
Blood and Lymphatic System Disorders	4 (5.1%)
Lymphadenopathy	3 (3.8%)
Cardiac Disorders	16 (20.5%)
Edema Lower Limb	7 (9.0%)
Edema NOS	3 (3.8%)
Ear and Labyrinth Disorders	4 (5.1%)
Earache	3 (3.8%)
Gastrointestinal Disorders	22 (28.2%)
Diarrhea NOS	10 (12.8%)
Vomiting NOS	7 (9.0%)
Nausea	6 (7.7%)
Constipation	3 (3.8%)
Taste Disturbance	3 (3.8%)
General Disorders and Administration Site Conditions	16 (20.5%)
Fatigue	3 (3.8%)
Injection Site Reaction NOS	3 (3.8%)
Musculoskeletal, Connective Tissue and Bone Disorders	21 (26.9%)
Arthralgia	7 (9.0%)
Back Pain	6 (7.7%)
Pain in Limb	4 (5.1%)
Nervous System Disorders	10 (12.8%)
Headache NOS	5 (6.4%)
Dizziness (exc. Vertigo)	4 (5.1%)
Renal and Urinary Disorders	9 (11.5%)
Renal Impairment NOS	3 (3.8%)
Respiratory, Thoracic and Mediastinal Disorders	20 (25.6%)
Cough	3 (3.8%)
Nasopharyngitis	3 (3.8%)
Sinusitis NOS	3 (3.8%)
Skin and Subcutaneous Tissue Disorders	11 (14.1%)
Pruritus NOS	3 (3.8%)
Vascular Disorders	10 (12.8%)
Hypertension Aggravated	4 (5.1%)
Hypotension NOS	4 (5.1%)

NOS=not otherwise specified.

a Patients could have received Venofer® and/or epoetin during the Extended Follow-Up Phase as needed to maintain a hemoglobin level between 11 and 12.5 g/dL, a TSAT of 25-50% and a ferritin level of 300-500 ng/mL.

Cross-reference: Appendix Table 6.3.2 and Appendix Listing 9.1.1

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 83

During the Extended Follow-Up Phase, at least one drug-related treatment-emergent adverse event was experienced by 20.5% (16/78) of the patients. The most commonly experienced drug-related treatment-emergent adverse events were taste disturbance (3.8%) and injection site burning (2.6%). None of the other drug-related events was experienced by more than 1 patient during the Extended Follow-Up Phase. A summary of drug-related treatment-emergent adverse events experienced by 3 or more patients during the Extended Follow-Up Phase is presented in the table below.

Table 6.6e Drug-Related Treatment-Emergent Adverse Events Experienced by 3 or More Patients During the Extended Follow-Up Phase (Safety Evaluable Population)

MedDRA SOC Preferred Term	Venofer®[a] (N=78)
At Least One Drug-Related Treatment-Emergent Adverse Event	16 (20.5%)
Gastrointestinal Disorders	5 (6.4%)
Taste Disturbance	3 (3.8%)

a Patients could have received Venofer® and/or epoetin during the Extended Follow-Up Phase as needed to maintain a hemoglobin level between 11 and 12.5 g/dL, a TSAT of 25-50% and a ferritin level of 300-500 ng/mL.

Cross-reference: Appendix Table 6.3.4 and Appendix Listing 9.1.1

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 84

During the Extended Follow-Up Phase, patients experienced treatment-emergent adverse events of headache (2.6%), hypertension aggravated (2.6%), hypertension (2.6%), and blood pressure fluctuation (1.3%) that were considered by the investigator to be related to epoetin administration.

During the Whole Study

A total of 91 patients were exposed to Venofer 200 mg either in treatment or extended follow-up phases. A summary of adverse events occurring in ≥5% of Venofer patients during the Treatment and Extended Follow-Up Phases is presented in the table below.

Table 8.6q Treatment-Emergent Adverse Events Experienced by ≥5% of Patients Treated with Venofer® During the Treatment and Extended Follow-Up Phases (Safety Evaluable Population; Study 1VEN99012)

MedDRA SOC Preferred Term	Oral Iron (N=48)	Venofer® (N=91)
At Least One Treatment-Emergent Adverse Event	**43 (89.6%)**	**77 (84.6%)**
Cardiovascular Disorders	8 (16.7%)	24 (26.4%)
Edema Lower Limb	2 (4.2%)	9 (9.9%)
Edema NOS	1 (2.1%)	6 (6.6%)
Gastrointestinal Disorders	23 (47.9%)	37 (40.7%)
Diarrhea NOS	5 (10.4%)	15 (16.5%)
Nausea	8 (16.7%)	12 (13.2%)
Vomiting NOS	6 (12.5%)	11 (12.1%)
Taste Disturbance	0	7 (7.7%)
General Disorders and Administration Site Conditions	5 (10.4%)	24 (26.4%)
Injection Site Burning	0	5 (5.5%)
Musculoskeletal, Connective Tissue and Bone Disorders	9 (18.8%)	25 (27.5%)
Arthralgia	2 (4.2%)	7 (7.7%)
Back Pain	2 (4.2%)	7 (7.7%)
Pain in Limb	0	5 (5.5%)
Nervous System Disorders	5 (10.4%)	16 (17.6%)
Headache NOS	1 (2.1%)	7 (7.7%)
Dizziness (excluding vertigo)	1 (2.1%)	6 (6.6%)
Vascular Disorders	5 (10.4%)	15 (16.5%)
Hypertension Aggravated	1 (2.1%)	7 (7.7%)

NOS=not otherwise specified.

Sponsor's table in NDA/SE1-008 submission Vol. 16, pp. 34

Reviewer's comments: Again, during the whole study period, more patients experienced adverse events including cardiovascular disorders, diarrhea, taste disturbance, muscular pain, headache, dizziness, and hypertension with Venofer treatment than with oral iron treatment. Patients experienced more nausea and vomiting with oral iron treatment than with Venofer treatment.

A summary of drug-related adverse events occurring in ≥2% of Venofer patients during the Treatment and Extended Follow-Up Phases is presented in the table below.

Table 8.6r Drug-Related Treatment-Emergent Adverse Events Experienced by ≥2% of Patients Treated with Venofer® or Oral Iron During the Treatment and Extended Follow-Up Phases (Safety Evaluable Population; Study 1VEN99012)

MedDRA SOC Preferred Term	Oral Iron (N=48)	Venofer® (N=91)
At Least One Drug-Related Treatment-Emergent Adverse Event	**19 (39.6%)**	**23 (25.3%)**
Endocrine Disorders	1 (2.1%)	0
Hypoglycemia NOS	1 (2.1%)	0
Gastrointestinal Disorders	17 (35.4%)	10 (11.0%)
Taste Disturbance	0	7 (7.7%)
Nausea	5 (10.4%)	2 (2.2%)
Constipation	7 (14.6%)	0
Vomiting NOS	4 (8.3%)	0
Abdominal Pain NOS	2 (4.2%)	0
Abdominal Distension	1 (2.1%)	0
Loose Stools	1 (2.1%)	0
Rectal Hemorrhage	1 (2.1%)	0
General Disorders and Administration Site Conditions	1 (2.1%)	10 (11.0%)
Injection Site Burning	0	5 (5.5%)
Injection Site Pain	0	2 (2.2%)
Fatigue	1 (2.1%)	0
Musculoskeletal, Connective Tissue and Bone Disorders	0	2 (2.2%)
Pain in Limb	0	2 (2.2%)
Nervous System Disorders	0	6 (6.6%)
Headache NOS	0	2 (2.2%)
Dizziness	0	2 (2.2%)
Skin and Subcutaneous Tissue Disorders	1 (2.1%)	2 (2.2%)
Pruritus NOS	0	2 (2.2%)
Dermatitis NOS	1 (2.1%)	0
Vascular Disorders	1 (2.1%)	0
Hypotension NOS	1 (2.1%)	0

NOS=not otherwise specified.

Sponsor's table in NDA/SE1-008 submission Vol. 16, pp. 35

Reviewer's comments: More gastrointestinal disorders including constipation, nausea, and abdominal pain were attributed to oral iron treatment by the investigators. Taste disturbance, injection site reactions, lamb pain, headache, dizziness, and pruritis were attributed to Venofer treatment by the investigators.

Deaths

One patient in the Venofer group died within 30 days after receiving study drug.
The patient was a 74-year-old male with a past medical history significant for hypertension, cardiomyopathy, atrial fibrillation, coronary artery disease, status-post myocardial infarction, peripheral vascular disease, and abdominal aortic aneurysm. Following randomization, the patient received Venofer 200 mg plus epoetin 2000 U during the Treatment Phase. The patient experienced 2 non-serious adverse events during the Treatment Phase (+2 edema on Day 8 and stiff neck on Day 35) that were considered by the Investigator to be not related to study medication. The patient entered the Extended Follow-Up Phase and received Venofer 200 mg plus epoetin 2000 U on Days 43 and 50. On Day — ne patient arrived at the Emergency Room

with no pulse, blood pressure or spontaneous respirations. Resuscitation efforts were unsuccessful. The cause of death was cardiopulmonary arrest secondary to coronary artery disease and hypertension. An autopsy was not performed. An ECG tracing performed on Day 43 demonstrated atrial fibrillation and probable old septal infarction. In the opinion of the investigator, the death was considered not related to Venofer.

None of the patients in the oral iron group died during the study or within 30 days after receiving study drug.

Serious Adverse Events

During the Treatment Phase, 7 (14.6%) patients in the Venofer group and 2 (4.2%) patients in the oral iron group experienced at least 1 serious adverse event. None of these serious adverse events was considered by the investigator to be related to study medication or epoetin administration. A summary of the patients who experienced serious adverse events during the Treatment Phase is presented in the table below.

Table 6.6f Patients Who Experienced Serious Adverse Events During the Treatment Phase (Safety Evaluable Population)

Patient Number	Age/Sex/ Race	Preferred Term	Relative Day[a]	Severity	Causality[b]	Treatment
Oral Iron						
04065	44/F/H	Patella fractured[c]		Moderate	None	Surgical
06101	61/M/A	Congestive cardiac failure		Moderate	None	Medication
Venofer®						
01001	27/F/B	Benign intracranial hypertension[c] (diagnosis: pseudotumor cerebri)		Severe	Unlikely	Surgical
01008	52/F/B	Pulmonary edema NOS[c]		Severe	None	Other
02521	78/F/B	Renal failure chronic[c]		Moderate	None	Other
03543	45/M/C	Diabetic ketoacidosis Fluid overload		Severe Severe	None None	Medication Medication
04069	70/M/C	Renal failure acute on chronic dialysis[c]		Moderate	None	Other
14262	71/F/C	Congestive cardiac failure Renal failure NOS Hypovolemia Congestive cardiac failure		Severe Moderate Severe Moderate	None None None None	Medication Medication Medication Medication
21082	43/M/C	Hyperglycemia NOS Upper gastrointestinal hemorrhage		Moderate Moderate	None None	Medication Medication

F=female; M=male; A=Asian; B=Black; C=Caucasian; H=Hispanic; NOS=not otherwise specified

a Day relative to first dosing day in Treatment Phase.

b As assessed by the Investigator.

c Event led to premature discontinuation.

Cross-reference: Appendix Listing 9.5.2

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 86

Reviewer's comments: The table shows that patients experienced more SAEs including congestive heart failure, pulmonary edema, fluid overload, hyperglycemia, renal failure, and benign intracranial hypertension with Venofer treatment than with oral iron treatment.

During the Extended Follow-Up Phase, 9 (11.5%) patients, including the patient who died, experienced at least 1 serious adverse event. None of the serious adverse events reported during the Extended Follow-Up Phase was considered by the investigator to be related to Venofer or epoetin administration. A summary of the patients who experienced serious adverse events during the Extended Follow-Up Phase is presented in the table below.

Table 6.6g Patients Who Experienced Serious Adverse Events During the Extended Follow-Up Phase[d] (Safety Evaluable Population)

Patient Number	Age/Sex/ Race	Preferred Term	Relative Day[a]	Severity	Causality[b]	Treatment
01006	28/F/B	Appendicitis		Moderate	None	Surgical
03048	52/F/C	Gastroenteritis NOS		Moderate	Unlikely	Other
04068	79/F/B	Accident NOS Dehydration		Moderate Moderate	Unlikely Unlikely	Surgical Medication
04561	59/M/C	Angina unstable		Severe	None	Other
02021	64/M/C	Renal failure chronic[c]		Severe	None	Other
04064	74/M/O	Cardiorespiratory arrest[c]		Severe	None	Other
08143	42/M/H	Renal failure chronic[c]		Moderate	Unlikely	Other
08149	65/M/H	Otitis externa NOS		Moderate	None	Medication
21082	43/M/C	Hip fracture[c] Metabolic acidosis NOS		Moderate Severe	None None	Surgical Other

F=female; M=male; B=Black; C=Caucasian; H=Hispanic; O=Other; NOS=not otherwise specified

a Day relative to first dosing day in Treatment Phase.

b As assessed by the Investigator.

c Event led to premature discontinuation.

d Patients could have received Venofer® and/or epoetin during the Extended Follow-Up Phase as needed to maintain a hemoglobin level between 11 and 12.5 g/dL, a TSAT of 25-50% and a ferritin level of 300-500 ng/mL.

Cross-reference: Appendix Listing 9.5.3

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 87

Reviewer's comments: It should be noted that one case of cardiorespiratory arrest and one case of unstable angina occurred during the extended follow-up phase with Venofer treatment. However, there was no comparator group during that time.

Other Significant Adverse Events

Premature Discontinuation due to Adverse Events

During Treatment Phase

One (2.1%) patient in the oral iron group and 6 (12.5%) patients in the Venofer group were prematurely discontinued from the study during the Treatment Phase due to the occurrence of adverse events. Of these patients, only 1 in the Venofer group experienced adverse events leading to premature discontinuation that were considered study drug-related (anxiety, headache, and nausea). A summary of the patients who experienced adverse events that led to premature discontinuation during the Treatment Phase is presented in the table below.

Table 6.6h Patients Who Experienced Adverse Events That Led to Premature Discontinuation During the Treatment Phase (Safety Evaluable Population)

Patient Number	Age/Sex/ Race	Preferred Term	Relative Day[a]	Severity	Causality[b]	Treatment
Oral Iron						
04065	44/F/H	Patella fractured	5	Moderate	None	Surgical
Venofer®						
01001	27/F/B	Benign intracranial hypertension (diagnosis: pseudotumor cerebri)	12	Severe	Unlikely	Surgical
01008	52/F/B	Pulmonary edema NOS	41	Severe	None	Other
02521	78/F/B	Renal failure chronic	6	Moderate	None	Other
04069	70/M/C	Renal failure acute on chronic dialysis	10	Moderate	None	Other
06602	60/F/H	Anxiety NEC Headache NOS Nausea	26 26 26	Mild Mild Mild	Possible Possible Possible	None None None
14262	71/F/C	Renal failure chronic	38	Moderate	None	Other

F=female; M=male; B=Black; C=Caucasian; H=Hispanic; NOS=not otherwise specified

a Day relative to first dosing day in Treatment Phase.

b As assessed by the Investigator.

Cross-reference: Appendix Listing 9.3.2

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 88

Reviewer's comments: More patients discontinued the treatment prematurely due to AEs in the Venofer group than in the oral iron group.

During Extended Follow-Up Phase

Eight (10.3%) patients were prematurely discontinued from the study during the Extended Follow-Up Phase due to the occurrence of adverse events. Of these patients, only 1 (1.3%) experienced adverse events leading to premature discontinuation that were considered study drug related (abrasion [excoriations on both arms]). A summary of the patients who experienced adverse events that led to premature discontinuation during the Extended Follow-Up Phase is presented in the table below.

Table 6.6i Patients Who Experienced Adverse Events That Led to Premature Discontinuation During the Extended Follow-Up Phase[c] (Safety Evaluable Population)

Patient Number	Age/Sex/ Race	Preferred Term	Relative Day[a]	Severity	Causality[b]	Treatment
01007	77/M/B	Anemia NOS aggravated	71	Severe	None	None
03046	42/F/H	Renal failure aggravated	68	Moderate	Unlikely	Other
09166	80/M/C	Abrasion NOS	65	Mild	Probable	Medication
02021	64/M/C	Renal failure chronic	108	Severe	None	Other
04064	74/M/O	Cardiorespiratory arrest	55	Severe	None	Other
08143	42/M/H	Renal failure chronic	70	Moderate	Unlikely	Other
08160	51/F/H	Menorrhagia	50	Moderate	None	None
21082	43/M/C	Hip fracture	100	Moderate	None	Surgical

F=female; M=male; B=Black; C=Caucasian; H=Hispanic; O=Other; NOS=not otherwise specified

a Day relative to first dosing day in Treatment Phase.

b As assessed by the Investigator.

c Patients could have received Venofer® and/or epoetin during the Extended Follow-Up Phase as needed to maintain a hemoglobin level between 11 and 12.5 g/dL, a TSAT of 25-50% and a ferritin level of 300-500 ng/mL.

Cross-reference: Appendix Listing 9.3.3

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 89

Reviewer's comments: It should be noted that an additional 10% of the patients who were enrolled in the extended treatment phase discontinued treatment prematurely due to AEs in the extended treatment period.

Hypersensitivity/Allergic Reactions

No case of hypersensitivity/allergic reactions were reported in the study.

Hypotension

During the Treatment Phase, 1 (2%) oral iron patient experienced hypotension that was considered unrelated to study drug. None of the Venofer patients experienced hypotension during the Treatment Phase. Four (5%) patients experienced hypotension during the Extended Follow-Up Phase. None of these events was considered related to study drug by the investigators.

Clinical Laboratory Evaluations

Mean Changes from Baseline in Laboratory Values

During Treatment Phase

Mean changes from baseline to Day 43 in hematology parameters are presented in the table below. Mean increases from baseline to Day 43 in MCV, MCH, reticulocytes, hemoglobin, and hematocrit were slightly higher in the Venofer group compared with the oral iron group. Mean changes from baseline to Day 43 in the other hematology parameters were similar between the treatment groups.

Table 6.6j Mean Changes From Baseline to Day 43 in Hematology Parameters (Safety Evaluable Population)

	Oral Iron (N=43)		Venofer® (N=39)	
Hematology Parameter (Units)	Mean Baseline (SD)	Change to Day 43 (SD)	Mean Baseline (SD)	Change to Day 43 (SD)
Basophils (%)	0.8 (0.47)	-0.1 (0.44)	1.0 (0.61)	-0.1 (0.84)
Eosinophils (%)	4.2 (2.92)	-0.8 (1.48)	4.1 (2.71)	-1.0 (2.12)
Hematocrit (%)	30.4 (2.11)	2.8 (3.00)	31.2 (2.08)	3.7 (3.12)
Hemoglobin (g/dL)	9.7 (0.70)	0.7 (0.97)	9.9 (0.60)	1.0 (0.98)
Lymphocytes (%)	22.4 (7.18)	0.7 (5.90)	21.4 (6.58)	-0.3 (5.00)
MCH (pg)	29.0 (2.14)	0.1 (1.07)	28.7 (2.04)	0.6 (1.32)
MCHC (g/dL)	32.5 (1.38)	-1.0 (1.42)	32.0 (1.44)	-0.7 (1.56)
MCV (fL)	89.2 (5.27)	3.0 (3.01)	89.5 (5.65)	4.2 (3.40)
Monocytes (%)	5.7 (1.61)	-0.2 (1.56)	5.6 (1.29)	-0.1 (1.72)
Neutrophils (%)	66.9 (8.61)	0.3 (7.36)	67.9 (7.86)	1.5 (6.27)
Platelets ($x10^9$/L)	257.9 (79.09)	-10.5 (36.05)	289.7 (102.93)	-11.3 (73.12)
Reticulocytes (%)[a]	2.7 (0.7)	0.1 (0.88)	2.8 (0.89)	0.5 (1.17)
WBC ($x10^9$/L)	7.0 (2.12)	-0.0 (1.32)	7.1 (1.77)	0.3 (1.22)

a N = 44 for oral iron group and N = 38 for Venofer® group.
Cross-reference: Appendix Table 7.1.2 and Appendix Listing 10.1

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 91

Mean changes from baseline to Day 43 in biochemistry parameters were generally small and not different between the treatment groups. The greatest change noted was an increase in mean glucose values, which occurred in both oral iron (18.8 mg/dL) and Venofer (32.1 mg/dL) groups. A summary of the mean changes from baseline to Day 43 in biochemistry parameters is presented in the table below.

Table 6.6k Mean Changes From Baseline to Day 43 in Biochemistry Parameters (Safety Evaluable Population)

	Oral Iron (N=44)		Venofer® (N=39)	
Biochemistry Parameter (Units)	Mean Baseline (SD)	Change to Day 43 (SD)	Mean Baseline (SD)	Change to Day 43 (SD)
ALT (U/L)	19.8 (18.21)	-1.3 (8.15)	17.7 (9.87)	0.1 (9.59)
AST (U/L)	20.6 (16.07)	-0.2 (5.08)	20.0 (5.93)	-1.2 (4.98)
Albumin (g/dL)	3.6 (0.36)	-0.0 (0.18)	3.7 (0.34)	0.0 (0.23)
Alkaline Phosphatase (U/L)	106.0 (40.50)	-6.0 (18.66)	120.8 (71.49)	0.3 (33.59)
Bicarbonate (mEq/L)	21.3 (3.53)	-0.1 (3.30)	21.0 (3.63)	-0.5 (3.31)
Calcium (mg/dL)	9.0 (0.72)	-0.1 (0.45)	8.9 (0.57)	-0.1 (0.43)
Chloride (mEq/L)	105.0 (4.83)	-0.5 (3.41)	105.0 (5.81)	-2.2 (6.32)
Creatinine (mg/dL)	3.5 (1.23)	0.2 (0.59)	3.5 (1.27)	0.2 (0.82)
GGT (U/L)	39.1 (53.64)	-1.4 (23.85)	36.5 (43.95)	3.1 (29.00)
Glucose (mg/dL)	127.4 (57.50)	18.8 (79.25)	130.6 (63.37)	32.1 (92.50)
LDH (U/L)	200.8 (44.93)	2.6 (29.23)	211.9 (36.13)	-7.1 (25.58)
Phosphate (mg/dL)	4.7 (0.82)	0.2 (0.92)	4.9 (1.12)	-0.2 (1.19)
Potassium (mEq/L)[a]	4.7 (0.53)	0.0 (0.58)	4.7 (0.56)	-0.1 (0.57)
Sodium (mEq/L)	139.4 (2.94)	-0.0 (2.79)	139.5 (3.52)	-1.5 (4.79)
Total Bilirubin (mg/dL)	0.3 (0.16)	-0.0 (0.13)	0.3 (0.20)	0.0 (0.12)
BUN (mg/dL)	57.6 (19.41)	2.7 (14.48)	60.7 (22.97)	6.1 (23.70)

a N = 38 for Venofer® group.

Cross-reference: Appendix Table 7.1.1 and Appendix Listing 10.1

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 92

During Extended Follow-Up Phase

Mean changes from baseline to Day 114 in hematology parameters are presented in the table below. Continued increases in hemoglobin, hematocrit, MCH, and MCV were noted.

Table 6.6l Mean Changes From Baseline to Day 114 in Hematology Parameters (Safety Evaluable Population)

	Venofer®[a] (N=64)	
Hematology Parameter (Units)	Mean Baseline (SD)	Change to Day 114 (SD)
Basophils (%)	0.8 (0.51)	-0.1 (0.56)
Eosinophils (%)	4.2 (3.01)	-1.1 (2.37)
Hematocrit (%)	30.6 (2.23)	5.2 (3.41)
Hemoglobin (g/dL)	9.8 (0.69)	1.6 (1.09)
Lymphocytes (%)	22.9 (7.23)	-0.8 (4.75)
MCH (pg)	28.7 (2.23)	1.1 (1.63)
MCHC (g/dL)	32.3 (1.33)	-0.4 (1.63)
MCV (fL)	88.7 (5.05)	4.6 (3.97)
Monocytes (%)	5.6 (1.48)	-0.1 (1.35)
Neutrophils (%)	66.5 (8.91)	2.1 (6.04)
Platelets ($x10^9$/L)	271.0 (97.54)	-20.5 (56.42)
Reticulocytes (%)	2.7 (0.71)	0.4 (1.01)
WBC ($x10^9$/L)	7.0 (1.98)	0.5 (1.27)

a Patients could have received Venofer® and/or epoetin during the Extended Follow-Up Phase as needed to maintain a hemoglobin level between 11 and 12.5 g/dL, a TSAT of 25-50% and a ferritin level of 300-500 ng/mL.

Cross-reference: Appendix Table 7.2.2 and Appendix Listing 10.1

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 93

Mean changes from baseline to Day 114 in biochemistry parameters were generally small. The greatest change noted was an increase in the mean glucose value (28.5 mg/dL). A summary of the mean changes from baseline to Day 114 in biochemistry parameters is presented in the table below.

Table 6.6m Mean Changes From Baseline to Day 114 in Biochemistry Parameters (Safety Evaluable Population)

	Venofer®[a] (N=64)	
Biochemistry Parameter (Units)	**Mean Baseline (SD)**	**Change to Day 114 (SD)**
ALT (U/L)	17.5 (9.50)	2.2 (9.80)
AST (U/L)	19.1 (6.20)	1.3 (6.76)
Albumin (g/dL)	3.7 (0.34)	-0.0 (0.22)
Alkaline Phosphatase (U/L)	109.1 (58.70)	9.0 (42.03)
Bicarbonate (mEq/L)	20.8 (2.82)	-0.9 (3.22)
Calcium (mg/dL)	9.0 (0.66)	-0.2 (0.48)
Chloride (mEq/L)	105.8 (4.55)	-1.6 (3.79)
Creatinine (mg/dL)	3.4 (1.08)	0.2 (0.66)
GGT (U/L)	33.1 (37.74)	5.2 (22.32)
Glucose (mg/dL)	132.1 (62.19)	28.5 (81.46)
LDH (U/L)	203.1 (42.23)	2.0 (30.31)
Phosphate (mg/dL)	4.7 (1.00)	0.1 (1.11)
Potassium (mEq/L)	4.7 (0.52)	-0.1 (0.60)
Sodium (mEq/L)	139.7 (3.01)	-0.7 (3.21)
Total Bilirubin (mg/dL)	0.3 (0.14)	0.0 (0.12)
BUN (mg/dL)	57.1 (19.92)	4.8 (17.03)

a Patients could have received Venofer® and/or epoetin during the Extended Follow-Up Phase as needed to maintain a hemoglobin level between 11 and 12.5 g/dL, a TSAT of 25-50% and a ferritin level of 300-500 ng/mL.

Cross-reference: Appendix Table 7.2.1 and Appendix Listing 10.1

Sponsor's table in NDA/SE1-008 submission Vol. 4, pp. 94

Shifts from Baseline

The incidences of shifts from baseline in hematology and biochemistry values during the Treatment Phase were generally comparable between the treatment groups. With respect to hematology values, greater proportions of patients in the Venofer group (23.1% and 30.8%, respectively) shifted from low hemoglobin and hematocrit values at baseline to normal values at Day 43 compared with the oral iron group (4.7% and 23.3%, respectively). A greater proportion of patients in the Venofer group also shifted from normal reticulocyte values at baseline to high values at Day 43 compared with the oral iron group (31.6% versus 20.5%). With respect to biochemistry values, a greater proportion of patients in the Venofer group shifted from normal GGT values at baseline to high values at Day 43 compared with patients in the oral iron group (15.4% versus 4.5%). A greater proportion of patients in the oral iron group shifted from low or normal glucose values at baseline to high values at Day 43 compared with the Venofer group (29.6% versus 18.0%). Additionally, greater proportions of patients in the oral iron group shifted

from normal phosphate values at baseline to high values at Day 43 compared with the Venofer group (18.2% versus 5.1%).

During the Extended Follow-Up Phase, notable shifts from normal baseline to Day 114 in biochemistry values were observed for albumin (15.6% shifted to low values), bicarbonate (15.6% shifted to low values), glucose (21.9% shifted to high values), and phosphate (15.6% shifted to high values). As an expected treatment effect, 45.3% and 34.4%, respectively, of the patients shifted from low hematocrit and hemoglobin values at baseline to normal values at Day 114. Additionally, 29.7% of the patients shifted from normal reticulocyte values at baseline to high values at Day 114.

Other Safety Parameters

Vital Signs
Small mean changes from baseline in vital sign parameters (heart rate, systolic blood pressure, diastolic blood pressure, temperature) and weight occurred over the course of the study in both treatment groups. No clinically meaningful trends were identified.

One patient in the oral iron group had an episode of mild hypotension on Day 10 that was considered by the investigator to be possibly related to study drug. No other adverse events associated with abnormalities in vital sign values reported during the Treatment or Extended Follow-Up Phases of the study were considered by the investigator to be study drug-related.

Physical Examination
Changes in physical examinations over the course of the study were observed in both treatment groups. The most common change in physical examination results was the development of edema. Edema was reported in 4 (8.3%) patients in the Venfer group and in 1 (2.1%) patients in the oral iron group.

Electrocardiograms
Thirty (30) of the 48 patients in the oral iron group and 26 of the 48 patients in the Venofer group had electrocardiograms performed at baseline. The majority of the patients in both treatment groups did not have electrocardiograms performed at the Day 43 Visit as it was not clinically indicated.

Among those patients who had electrocardiograms performed at baseline and at the Day 43 Visit, only 1 patient with a normal evaluation at baseline had an abnormal finding at the Day 43 Visit. The patient in the oral iron group had electrocardiogram findings at the Day 43 visit that were suggestive of hypertensive cardiovascular disease, which the investigator considered to be clinically significant. Specific details regarding the abnormal findings were not reported.

Subgroup Analyses

Subgroup analyses of safety data by demographics, disease characteristics, or concomitant medications were not performed for the trial.

Safety Comparison between CKD Patients Not On Dialysis and Those Undergoing Hemodialysis in Clinical Studies

Five studies have been conducted in CKD patients undergoing hemodialysis and the safety information from these studies has been included in the current labeling. The following table shows the drug-related adverse events judged by investigators reported by more than one patient from Study 1VEN99012 in CKD patients not on dialysis and studies in CKD patients undergoing hemodialysis.

Table 8.6o Drug-Related Adverse Events Experienced by 1 or More Patients (Safety Evaluable Population; Study 1VEN99012, VIFOR/100, LU98001, LU98002, 1VEN99010, and 1VEN01015)

	CKD Patients[a] Not Receiving Dialysis	CKD Patients Receiving Dialysis		
Drug-Related Adverse Event	200 mg Undiluted (N=48)	200 mg Undiluted (N=194)	100 mg Undiluted (N=765)	100 mg Diluted (N=131)
TasteDisturbance/ Perversion	4 (8.3%)	9 (4.6%)	11 (1.4%)	0
Injection Site Burning	3 (6.3%)	0	0	0
Nausea	2 (4.2%)	0	2 (<1%)	4 (3.0%)
Dizziness	2 (4.2%)	0	0	0
Pruritis	1 (2.1%)	1 (<1%)	3 (<1%)	1 (<1%)
Constipation	0	0	4 (<1%)	0
Diarrhea	0	1 (<1%)	3 (<1%)	0
Abdominal Pain/Cramping	0	2 (1.0%)	1 (<1%)	1 (<1%)
Hypotension	0	0	3 (<1%)	17 (13.0%)
Elevated Liver Enzymes	0	0	0	2 (1.5%)
Vomiting	0	0	2 (<1%)	2 (1.5%)
Pneumonia	0	0	0	2 (1.5%)

a Drug-related events reported during the Treatment Phase.

Sponsor's table in NDA/SE1-008 submission Vol. 16, pp. 29

Taste disturbance/perversion is the most frequently reported adverse event among CKD patients undergoing hemodialysis or not on dialysis that were treated with Venofer. The incidence tends to be higher with the 200 mg dose than with the 100 mg dose, and somewhat higher among CKD patients not on dialysis than CKD patients undergoing dialysis.

Reviewer's comments: It seems that more AEs including taste disturbance/perversion, nausea, dizziness, and pruritus were attributed to Venofer treatment in this trial in CKD patients not on dialysis than in study in CKD patients on dialysis by investigators.

Adverse Events from Sources Other Than Clinical Trials

Published Literature

Three studies have been published to date to evaluate the effects of Venofer in anemic chronic renal failure patients not receiving dialysis. Two of these were reported by the same author in Israel.

1. Silverberg DS, Iaina A, Peer G, et al. Intravenous iron supplementation for the treatment of the anemia of moderate to severe chronic renal failure in patients not receiving dialysis. Am J Kidney Dis 1996; 27: 234-8.

Silverberg et al. (1996) reported 33 predialysis patients with moderate to severe CKD (creatinine clearance 10-40 mL/min) who were anemic despite oral iron supplementation received Venofer 200 mg/month for 5 months. Almost all of the patients were hypertensive at baseline (32/33). Four patients necessitated a slight adjustment in their BP medication during the study. No other adverse events were reported. There were no significant changes in mean serum creatinine, creatinine clearance, systolic BP, or diastolic BP.

2. Silverberg DS, Blum M, Agbaria Z, et al. The effect of IV iron alone or in combination with low-dose erythropoietin in the rapid correction of anemia of CRF in the predialysis period. Clin Nephrol 2001; 55(3): 212-9.

A randomized study by Silverberg et al. (2001) evaluated the effect of Venofer 200 mg IV with or without 2000 IU erythropoietin (EPO) given once weekly for 5 doses in 90 predialysis patients with CRF (creatinine clearance 10-40 mL/min/1.73 m^2). No adverse events were reported and no significant changes in systolic or diastolic BP were identified. In the 12-month follow-up period, a small but significant increase in mean serum creatinine was observed. Comparison of the rate of change in the glomerular filtration rate during 1-2 years before the study to the rate of change during the 12-month follow-up period suggested a slowing of the progression of renal failure.

3. Stoves J, Inglis H, Newstead CG. A randomized study of oral vs. intravenous supplementation in patients with progressive renal insufficiency treated with erythropoietin. Nephrol Dial Transplant 2001; 16: 967-74.

Venofer 300 mg IV monthly was compared with oral ferrous sulfate 200 mg in a 6-month randomized study of anemic patients with progressive renal insufficiency not on dialysis. All patients also received recombinant human erythropoietin (rHuEpo) subcutaneously at an initial dose of 2000 U twice weekly. Patients were followed for an average of 5.2 months. Three possible allergic reactions (urticaria rashes, abdominal pain, arthragia, myalgia, nausea, headache, paraesthesia and loss of consciousness) to Venofer occurred in 3 women with low body mass. Study drug was eventually permanently discontinued in all 3 patients. Oral iron was discontinued in 1 patient due to severe constipation.

Post-Marketing Data

According to Periodic Safety Update Reports (PSUR) issued by the manufacturer of Venofer, Vifor (International) Inc, in Switzerland. Among the estimated 912,178 patients who received

Venofer between 1 September 2001 through 28 February 2003, 167 patients reported a total of 465 adverse events that were considered at least possibly related to Venofer. This number does not include events that occurred in the clinical studies or publications discussed above.

A total of 178 serious adverse events (114 listed and 64 unlisted) have been reported during that period. No deaths related to Venofer were reported. The most common serious adverse events reported included hypotension (39), anaphylactoid reaction (12), dyspnea (8), sweating increased (8), injection site thrombosis (8), urticaria (7), and abdominal pain (6).

There were 287 non-serious adverse events (188 listed and 99 unlisted) reported during this report period. The most common non-serious adverse events reported included hypotension (25), abdominal pain (21), nausea (21), vomiting (18), flushing (17), increased sweating (13), chest pain (12), pruritus (9), feeling hot (9), dyspnea (8), headache (8), urticaria (8), and anaphylactoid reaction (7).

Overall, 19 anaphylactoid reactions (12 serious and 7 non-serious) have been reported between 1 September 2001 through 28 February 2003.

Safety Update

The sponsor submitted the 12th of a series of Periodic Safety Update Reports (PSUR) issued by the manufacturer of Venofer, Vifor (International) Inc. This PSUR summarized the safety data received by Vifor (International) Inc. from worldwide sources from March 1, 2003 to August 31, 2003.

Venofer was first approved in 1950 in Switzerland. From 1950 to August 2003, it has received regulatory approval for marketing authorization in 69 countries worldwide.

Patient Exposure

Clinical trials

The number of patients exposed in clinical trials has been obtained from monitoring and status reports and publications. From 1 March 2003 to 31 August 2003, 1008 patients were exposed to Venofer in clinical trials. These patients included 22 with pre-dialysis CKD, 32 with peritoneal dialysis, 301 with hemodialysis (HD), 60 pregnant women, 1 with heart failure, 460 with preoperative status, 37 with cancer, 70 with inflammatory bowel disease (IBD) and 25 with iron deficiency.

Market experience

The estimated patient exposure was 482,177 patient years based on 9,643,525 ampoules (containing 100 mg iron each) have been sold in the period between 1 March 2003 to 31 August 2003, assuming that one patient requires 20 ampoules Venofer (containing 100 mg iron each) per year. For countries to which Vifor (International) Inc. has only delivered the active ingredient

and not the final product (ampoules), the number of ampoules sold has been estimated assuming that 10 % of the delivered iron is lost during the manufacturing process of the final product.

Overall Safety Evaluation

Among the 482,177 patient years use of Venofer between 1 March 2003 and 31 August 2003 based on the estimation from market exposure, 41 patients were reported to have experienced 121 adverse reactions considered at least "possibly related" to Venofer. A review of all the 121 events indicated that 91 reactions were listed (38 serious, 53 non-serious), 30 reactions were unlisted (14 serious, 16 non-serious).

Regarding the serious and listed cases, no particular change or trend in severity, outcome or involved populations was observed. A total of 38 adverse reactions were reported in 14 patients. There were three reactions considered life-threatening; all patients fully recovered. The symptoms were: dyspnea (5), anaphylactoid reaction (4), hypotension (4), chest pain (3), rash (2), circulatory collapse (2), edema peripheral (2), edema (2), flushing (1), skin discoloration (1), erythema (1), urticaria (1), chest tightness (1), pyrexia (1), joint swelling (1), nausea (1), vomiting (1), depressed level of consciousness (1), paraesthesia (1), coma (1), type I hypersensitivity (1), and injection site extravasation (1).

There was no particular evolution regarding the non-serious and listed events. A total of 53 adverse reactions were reported in 24 patients. There were two anaphylactoid reactions. The other events were nausea (5), vomiting (5), rash (4), hypotension (3), dizziness (3), pruritus (3), abdominal pain (2), malaise (2). pyrexia (2), edema peripheral (2), arthralgia (2), burning sensation (2), injection site extravasation (2), dyspnea (2), flushing (1), rigors (1), anasarca (1), chest tightness (1), pain (1), paraesthesia (1), loss of consciousness (1), throat tightness (1), rash macular (1), rash pruritic (1), injection site warmth (1), and injection site swelling (1).

In total, six anaphylactoid reactions (4 serious and 2 non-serious) have been reported during this 6-month period.

There were 14 serious and unlisted adverse reactions, involving 8 patients. In five of these eight patients only some symptoms had to be considered unlisted but the main symptom and the event as a whole was considered serious and listed. Out of the remaining three cases two ended with fatal outcomes (Epidermal necrosis, Steven Johnson Syndrome in one patient, and collapse and ischemic enterocolitis in another patient) which were considered by the manufacturer not to be related to Venofer because the first patient was also on other unspecified drugs and the second patient had thrombus in superior mesenteric artery identified by the autopsy. These two cases were reported by the health authorities from Great Britain and the Netherlands, respectively.

There were 9 patients experiencing 16 non-serious and unlisted adverse reactions during the report period: back pain (3), blood pressure decreased (3), sweating increased (2), cold sweat (1), dry mouth (1), blood pressure increased (1), hyperventilation (1), dysphonea (1), face edema (1), hypophosphatemia (1), and injection site stinging (1).

Two cases of suspected overdoses (> 7mg iron/kg body weight) were reported, both from the USA and involving two pregnant women. No abuse but three cases of misuse (para-venous application) was observed during the period.

There were 1008 newly included patients in clinical trials or reported in the literature in the period from 1 March 2003 to 31 August 2003. In the literature, 10 patients experiencing 12 adverse reactions were reported. All reactions were non-serious and listed: phlebitis (3), rigors (2), asthenia (2), dyspnea (2), rash (2), and abdominal pain (1). During the pharmacokinetic study (FARMOVS 115/ 01/ Sponsor Study No. IS-PK500) the following adverse reactions were reported: non-serious and listed including headache (7), edema peripheral (5), abdominal pain (2), nausea (1), vomiting (1), urticaria (1) and pruritus (1), and non-serious and unlisted including back pain (2) and orthostatic hypotension (1).

The major safety issue with Venofer remains the occurrence of anaphylactoid reactions. There were 6 spontaneously reported anaphylactoid reactions that were newly reported in this PSUR.

D. Adequacy of Safety Testing

Only one study (Study 1VEN99012) was conducted in CKD patients not on dialysis by the sponsor. In this study, 48 patients were exposed to Venofer 200 mg by slow injection over 5 minutes for about 5 doses during the treatment phase and 78 patients were exposed to Venofer 200 mg for about 5 doses during the extended phase of the study. A total of 91 patients with CKD not on dialysis were exposed to Venofer 200 mg doses administered over 5 minutes in the study.

Currently approved dose regimen for CKD patients undergoing hemodialysis is Venofer 100 mg by slow injection over 5 minutes or diluted infusion over at least 15 minutes for 10 doses during dialysis session.

It has been recognized that rapid administration and larger dose administration are associated with more AEs with intravenous iron products (Bastabni B. et al, Nephrology 2003 Vol. 8: 8-10; Parkkinen J. et al, Nephrol Dial Transplant 2000, Vol. 15:1827-34; Zanen AL et al, Neprol Dial Transplant 1996, Vol. 11:820-4). The manufacturer of Venofer, Vifor (International) Inc. has recommended that the rate of administration of Venofer should not be more than 20 mg /min. The rate of administration of Venofer used in the trial was 40 mg/min. In the trial, more AEs (except for gastrointestinal disorders), SAEs and premature discontinuations due to AEs were observed in Venofer-treated patients than oral iron-treated patients. Considering a high dose with more rapid administration of Venofer for a new population, more safety data (about a total of 200 patients) should be collected to support the safety for Venofer with the new dose regimen in CKD patients not on dialysis.

E. Summary of Critical Safety Findings and Limitations of Data

Only one study (Study 1VEN99012) was conducted in CKD patients not on dialysis by the sponsor. In this study, 48 patients were exposed to Venofer 200 mg by slow injection over 5

minutes for about 5 doses during the treatment phase and 78 patients were exposed to Venofer 200 mg for about 5 doses during the extended phase of the study. A total of 91 patients with CKD not on dialysis were exposed to Venofer 200 mg doses administered over 5 minutes in the study.

The overall incidences of treatment-emergent adverse events were similar between the Venofer group (87.5%, 42/48) and the oral iron group (89.6%,43/48) during the treatment phase. However, patients in the Venofer group experienced more cardiovascular, endocrine, general and administration site, nervous system, and vascular disorders than in the oral iron group while patients in the oral iron group experienced more gastrointestinal (except for taste disturbance and diarrhea) and skin and subcutaneous tissue disorders than in the Venofer group. Gastrointestinal disorders were the most commonly experienced treatment-emergent adverse events in both treatment groups (47.9% in the oral iron group and 35.4% in the Venofer group). AEs that occurred more frequently with Venofer treatment than with oral iron treatment included edema (8.3% vs. 2.1%), hyperglycemia (8.3% vs. 0%), taste disturbance (8.3% vs. 0%), dizziness (8.3% vs. 2.1%), hypertension aggravated (8.3% vs. 2.1%), and injection site burning (6.3% vs. 0%). AEs occurred more frequently with oral iron treatment than with Venofer treatment included nausea (16.7% vs. 12.5%) vomiting (12.5% vs. 8.3%), constipation (14.6% vs. 2.1%), pruritus (12.5% vs. 2.1%), abdominal pain (6.3% vs. 2.1%), weakness (6.3% vs. 0%), and nasal congestion (6.3% vs. 2.1%).

During the Extended Follow-Up Phase, at least one treatment-emergent adverse event was experienced by 78.2% (61/78) of the patients. The most commonly experienced treatment-emergent adverse events were diarrhea (12.8%), vomiting (9.0%), edema lower limb (9.0%), and arthralgia (9.0%).

During the whole study period, patients experienced more adverse events including cardiovascular disorders, diarrhea, taste disturbance, muscular pain, headache, dizziness, and hypertension with Venofer treatment than with oral iron treatment. Patients experienced more nausea and vomiting with oral iron treatment than with Venofer treatment.

More gastrointestinal disorders including constipation, nausea, and abdominal pain were attributed to oral iron treatment by the investigators. Taste disturbance, injection site reactions, limb pain, headache, dizziness, and pruritis were attributed to Venofer treatment by the investigators.

One patient died at 5 days after the last Venofer dose during the Extended Follow-Up Phase. The patient was a 74-year-old male with significant cardiac history who received Venofer 200 mg during the Treatment Phase and 2 additional Venofer doses in the extended follow-up. The patient experienced 2 non-serious adverse events during the Treatment Phase (+2 edema on Day 8 and stiff neck on Day 35) that were considered by the Investigator to be not related to study medication. The cause of death was attributed to cardiopulmonary arrest secondary to coronary artery disease and hypertension and was considered unrelated to Venofer by the investigator. None of patients in the oral iron group died during the study and within 30 days after receiving study drug.

During the Treatment Phase, 7 (14.6%) patients in the Venofer group and 2 (4.2%) patients in the oral iron group experienced at least 1 serious adverse event. More patients experienced more SAEs including congestive heart failure, pulmonary edema, fluid overload, hyperglycemia, renal failure, and benign intracranial hypertension with Venofer treatment than with oral iron treatment. None of these serious adverse events was considered by the investigator to be related to study medication.

More patients discontinued the treatment prematurely due to AEs in the Venofer group (12.5%) than in the oral iron group (2.1%) during the treatment phase. An additional 10% of patients who have enrolled in the extended treatment phase prematurely discontinued the treatment due to adverse events.

No cases of hypersensitivity/allergic reaction were reported with Venofer treatment in the study. One case of hypotension was reported with oral iron treatment. No case of hypotension was reported during the treatment phase and 4 (5%) cases of hypotension were reported during the Extended Follow-Up Phase. None of these events was considered related to study drug by the investigators.

Only 3 published papers on studies in patients with CKD not on dialysis were found in the literature search. Safety information from these studies was limited.

Most adverse events reported by post-marketing spontaneous reports have been included in the current labeling.

In conclusion, there is limited safety information for Venofer in CKD patients not on dialysis. Clinical study 1VEN99012 showed that patients experienced more adverse events (except for gastrointestinal disorders), serious adverse events, and premature discontinuation due to adverse events with Venofer treatment than with oral iron treatment.

VIII. Dosing, Regimen, and Administration Issues

The current recommended dosing regimen of Venofer is 100mg iron (5mL) by slow IV injection over 5 minutes or IV infusion as diluted solution over at least 15 minutes for treatment of iron deficiency anemia in patients undergoing chronic hemodialysis on erythropoietin.

The proposed new dosing regimen for treatment of chronic kidney disease not on dialysis is Venofer 200 mg by IV injection over 5 minutes weekly for 5 doses. The proposed rate of administration of Venofer 200 mg dose is Rapid administration and larger dose administration have been associated with more AEs (Bastabni B. et al, Nephrology 2003 Vol. 8: 8-10; Parkkinen J. et al, Nephrol Dial Transplant 2000, Vol. 15:1827-34; Zanen AL et al, Neprol Dial Transplant 1996, Vol. 11:820-4). The manufacturer of Venofer, Vifor (International) Inc. has recommended that the rate of administration of Venofer should not be more than 20 mg/min.

For efficacy, Study 1VEN90912 failed to demonstrated that Venofer 200 mg IV is superior to oral iron in increase in hemoglobin at Day 43 from baseline (1.0 g/dL vs. 0.7 g/dL, p=0.14).

For safety, patients experienced more adverse events (except for gastrointestinal disorders), serious adverse events, and premature discontinuation due to adverse events with Venofer treatment than with oral iron treatment.

To support the proposed higher dose with more rapid administration of Venofer for a new population, more safety data (about a total of 200 patients) should be collected to support the safety for Venofer with the new dose regimen in CKD patients not on dialysis possibly in a new trial designed to demonstrate the effectiveness of Venofer in this population.

In conclusion, the proposed new dose regimen is not adequately supported by the submitted efficacy and safety data. An additional adequate and well-controlled study will be needed to support the proposed new dose regimen.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Gender

There were 19 males and 29 females who received Venofer 200 mg dose in Study 1VEN90912 in the Treatment Phase. The mean increase in hemoglobin at Day 43 in the Venofer group was 0.8 g/dL in men (17 were available) and 1.2 g/dL in women (22 were available) as compared to the oral iron group (1.0 g/dL and 0.6 g/dl, respectively). It seems that women responded to Venofer better in increase in hemoglobin level than men based on a limited number of patients available. The mean increase in ferritin at Day 43 was 299 ng/mL in men (17 were available) and 280 ng/mL in women (22 were available) as compared to the oral iron group (-4.4 ng/mL and -5.4 ng/mL, respectively). There was no difference in increase in ferritin level between men and women.

The gender effect on safety of Venofer 200 mg was not analyzed by the sponsor.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Age

There were 22 patients with age <65 years and 26 patients with age ≥65 years who received Venofer 200 mg dose in Study 1VEN90912. The mean increase in hemoglobin at Day 43 in the Venofer group was 0.8 g/dL in patients <65 years (17 were available) and 1.2 g/dL in patients ≥65 years (22 were available) as compared to the oral iron group (0.6 g/dL and 0.9 g/dl, respectively). The mean increase in ferritin at Day 43 was 261 ng/mL in patients <65 years (17 were available) and 309 ng/mL in patients ≥65 years (22 were available) as compared to the oral iron group (0.4 ng/mL and -14 ng/mL, respectively). This suggests that patients with age ≥65

years responded to Venofer better in increase in hemoglobin and ferritin levels than those with age <65 years, based on the limited number of patients available.

The age effect on safety of Venofer 200 mg was not analyzed by the sponsor.

Race
There were 18 Caucasian, 11 Black and 19 other races (17 Hispanic and 2 Asian) patients who received Venofer 200 mg dose in the Treatment Phase in Study 1VEN90912. The mean increase in hemoglobin at Day 43 in the Venofer group was 0.7 g/dL in Caucasian (15 were available), 0.4 in Black (6 were available), and 1.5 g/dL in other races (18 were available) patients as compared to the oral iron group (1.0 g/dL, 0.1 g/dL and 0.9 g/dl, respectively). The mean increase in ferritin at Day 43 in the Venofer group was 305 ng/mL in Caucasian (15 were available), 237 ng/mL in Black (6 were available), and 290 ng/mL in other races (18 were available) patients as compared to the oral iron group (-15 ng/mL, 1.9 ng/mL, and 5.9 ng/mL, respectively). No conclusion on race effect can be made because of the limited number of patients available in the study.

The race effect on safety of Venofer 200 mg was not analyzed by the sponsor.

Renal impairment
All study patients had chronic kidney disease not on dialysis (creatinine clearance <40 mL/min).

Hepatic impairment
No study was performed in patients with hepatic impairment.

Pregnancy
No study was performed in pregnant subjects.

C. Evaluation of Pediatric Program

A pharmacokinetic study of Venofer in adolescents was completed and submitted to the Agency for review. An efficacy and safety study of Venofer in pediatric population (2 to 12 years) for treatment of iron deficiency anemia in patients undergoing chronic dialysis is ongoing. Both studies are Phase 4 commitments.

D. Comments on Data Available or Needed in Other Populations

There are no comments regarding other populations.

X. Conclusions and Recommendations

A. Conclusions

The current application failed to demonstrate that Venofer 200 mg IV by slow injection over 5 minutes for 5 doses is superior to oral iron (ferrous sulfate) 325 mg 3 times a day for 29 days for

treatment of anemia in patients with chronic kidney disease not on dialysis. The safety evaluation showed more serious adverse events, premature discontinuations due to adverse events with Venofer treatment than with oral iron treatment. From a clinical prospective, the potential benefit of Venofer 200 mg IV by slow injection over 5 minutes for 5 doses does not outweigh the risk for treatment of iron deficiency in patients with chronic kidney disease not on dialysis based on the submitted data.

B. Recommendations

From a clinical perspective, this reviewer recommends Venofer is not approvable for the proposed indication expansion from "treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy" to "treatment of iron deficiency anemia in chronic kidney disease (CKD) patients on erythropoietin".

The clinical deficiencies include the following:

1. Only one study was conducted in patients with chronic kidney disease not on dialysis. The study failed to demonstrate that Venofer is superior to oral iron in an increase in hemoglobin at Day 43 from baseline as planned in the study protocol. The primary efficacy results showed that the difference in mean change in hemoglobin from baseline between Venofer and oral iron groups was not statistically significant (1.0 g/dL vs. 0.7 g/dL, p=0.14).
2. Initiation of epoetin therapy in the majority of study patients (83% in the Venofer group and 90% in the oral iron group) in the study may have contributed significantly to an increase in hemoglobin at Day 43 from baseline in both treatment groups.
3. A significant proportion of randomized patients were not included in the primary efficacy analysis in the study [26 % (14/53) in the Venofer group and 12% (6/49) in the oral iron group)].
4. In the study patients in the Venofer treatment group experienced more adverse events (except for gastrointestinal disorders), serious adverse events, and premature discontinuation due to adverse events than did patients in the oral treatment group.
5. Safety information in chronic kidney disease patients not on dialysis is limited.

To resolve the clinical deficiencies, the sponsor should conduct an adequate and well-controlled study to support the efficacy and safety of Venofer for the treatment of iron deficiency in chronic kidney disease patients not on dialysis. The study should be a randomized, parallel groups controlled study. The study patients should be patients who have received epoetin therapy with a stable dose for at least 3 months before the study and who will maintain the previous epoetin dose as much as possible during the study.

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Kathy Robie-Suh
6/8/04 07:44:42 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-135 / S-008

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW 1	1. Organization: HFD-180	2. NDA Number: 21-135	
3. Name and Address of Applicant (City & State): Luitpold Pharmaceuticals, Inc. One Luitpold Drive Shirley, NY 11967		4. AF Number: 5. Supplement(s):	
6. Name of Drug: Venofer®	7. Nonproprietary Name: Iron Sucrose Injection (USP)	Numbers SE1-008	Dates August 15, 2003
8. Supplements Provide for: The establishment of a 200 mg dose of Venofer® in the management of anemia in patients receiving erythropoietin for chronic kidney disease (CKD) not undergoing hemodialysis.		9. Amendments and Other (Reports, etc.) Dates: BC: February 25, 2004	
10. Pharmacological Category: Hematinic	11. How Dispensed: R_X X OTC	12. Related IND/NDA/DMF(s):	
13. Dosage Form: Injection	14. Potency: 20 mg iron/mL		
15. Chemical Name and Structure: Exact structure unknown. Estimated: $[Na_pFe_5O_8(OH)_r \cdot x(H_2O)]_L \cdot m(C_{12}H_{22}O_{11})$ Where: p = 2.30 ≈ 2; r = 1.3 ≈ 1; x = 2.70 ≈ 3; L = degree of iron polymerization; m = number of sucrose molecules associated with iron (III) hydroxide.		16. Records and Reports: Current Yes No Reviewed Yes No	
17. Comments: cc: NDA 21-135 HFD-180/Div File HFD-181/TClayton HFD-180/LZhou HFD-180/RFrankewich			
18. Conclusions and Recommendations: From a CMC perspective, this supplement may be approved.			
19.Reviewer			
Name: Raymond Frankewich, Ph.D.	Signature	Date Completed: March 18, 2004	

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-135 / S-008

ENVIRONMENTAL ASSESSMENT

CLAIM FOR CATEGORICAL EXCLUSION OF NEED TO FILE AN ENVIRONMENTAL ASSESSMENT

Pursuant to 21 C.F.R. §§ 25.31(b) and (c), Luitpold claims that this supplement qualifies for a categorical exclusion of the need to file an Environmental Assessment under both subsections since (1) the estimated concentration of the active moiety, iron, to be produced in any of the next five years (which is [redacted] of iron ([redacted] of iron sucrose]) at the point of entry into the aquatic environment will be less than 1 ppb (see attached calculation) and (2) the active moiety, iron, occurs naturally in the environment and the approval of this supplement for an additional use will not alter significantly the concentration or distribution of iron, its metabolites or degradation products in the environment.

Peter S. Reichertz
Agent

CALCULATION FOR VENOFER ENVIRONMENTAL ASSESSMENT

Based on a value of [redacted] emental iron per year the calculation for Venofer's expected introduction concentration (EIC) is as follows:

EIC - Aquatic (ppb) = [redacted] =

[redacted] ppb elemental iron

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-135 / S-008

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation
CLINICAL STUDIES

NDA:	21-135/S-008 (2nd Cycle)
Name of drug:	Venofer (iron sucrose injection)
Applicant:	Luitpold Pharmaceuticals, Inc.
Indication:	Treatment of iron deficiency anemia for chronic renal failure patients (CRF) who are not on dialysis
Documents reviewed:	Volumes 1-50, dated December 17, 2004
Project manager:	Alice Kacuba
Clinical reviewer:	Andrew Dmytrijuk, M.D.
PDUFA Goal Date:	June 17, 2005
Statistical reviewer:	Mushfiqur Rashid, Ph.D.
Statistics team leader:	Stella Grosser, Ph.D.
Biometrics division director:	S. Edward Nevius, Ph.D.

Keywords: NDA review, clinical studies, safety studies, Fisher's exact test

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The sponsor submitted this NDA (21-135/SE1-008/AZ; 2nd review cycle) as a major amendment to support a previously submitted NDA (21-135/SE1-008) with the indication of the use of Venofer (iron sucrose injection) 200 mg dose (200 mg for five weeks) plus erythropoietin in the management of anemia patients receiving erythropoietin for chronic kidney disease (CKD) not undergoing dialysis. In the previous submission, the change in hemoglobin from baseline to day 43 was not statistically significant (p-value=0.14) between the Venofer and oral iron treated group. The sponsor was issued a non-approvable letter on June 18, 2004. The FDA noted that in its review that erythropoietin was initiated concurrently with iron in the majority of subjects. Any effect of iron may have been confounded by the concomitant initiation of erythropoietin.

The current submission also does not provide statistically persuasive results (p-value 0.03 by primary analysis; p-value 0.05 by logistic regression analysis; p-value 0.16 of Cochran-Mantel-Haenszel test) with respect to the primary endpoint (Perecnt of subjects with $\geq$ 1.0 g/dL hemoglobin increase from baseline) when considered as a single study. However, this is an active control study with oral iron as a comparator. The oral iron has an effect of increasing hemoglobin in general. The medical review should address this issue in depth.

The incidence of any specific treatment related adverse events were comparable between the two groups except the incidence of gastro-intestinal disorders (9% Venofer and 18% oral iron).

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

Venofer was originally approved for ESRD (end stage renal disease) patients on the basis of 100 mg of iron sucrose injection given over 5 minutes per dialysis session and up to a total 1000 mg dose for each treatment cycle. The previous non-approved submission of Venofer, administered 200 mg for five weeks, was proposed for CRF patients who were not on dialysis. The efficacy data from the previous non-approved submission did not adequately show that Venofer 200 mg is effective in increasing hemoglobin level of CRF patients who are not on dialysis.

The current submission consists of a single study (study 1VEN03027) and is for CRF patients without dialysis. It is a the major amendment to the previous study.

Study 1VEN03027 was a randomized, open-label, multicenter, active control study of intravenous iron sucrose (Venofer 1000 mg in divided doses over a 14-day period) versus oral iron (325 mg ferrous sulfate 3 times daily x 56 days) in non-dialysis dependent chronic kidney disease (NDD-CKD) subjects. Eligible subjects were separated by erythropoietin use, stratified within these subgroups by gender and baseline hemoglobin, and randomized in 1:1 ratio within each combination of strata. A total of one hundred eight two subjects were randomized (ninety one patients in oral iron group and ninety one) patients in Venofer group.

1.3 STATISTICAL ISSUES AND PRINCIPAL FINDINGS

The primary objective of this study was to assess the comparative efficacy endpoint of two forms of iron therapy, parenterally administered Venofer and oral ferrous sulfate, each independent of hemoglobin response to erythropoietin. Concurrent initiation of erythropoietin and iron confounds analysis of the hemoglobin effect of either drug. Therefore, in this study erythropoietin was maintained at a stable dose for at least 8 weeks before iron therapy was permitted to participate to maximize its effect.

The sponsor reported that the current submission (NDA 21-135/SE1-008/AZ; 2nd review cycle) was designed by Luitpold Pharmaceutical Inc. to distinguish iron effects from those of erythropoietin by requiring stable erythropoietin to be administered for a prolonged period prior to randomization. The new design also sought to evaluate the potential role of the intravenous administration of iron in both the erythropoietin and non-erythropoietin treated populations. Note that this study was planned before the sponsor received the non-approval letter for the original submission . This submission addresses the efficacy and safety data in support of the intravenous use of Venofer (iron sucrose injection) 1000 mg in divided dose of 1000 mg a 14-day period (either 500 mg infusion on days 0 and 14 or 200 mg injection on five different occasions within the 14-day period) in chronic renal failure (CRF) patients who are not on dialysis.

The primary measure of efficacy compared the proportion of subjects with a hemoglobin level increase of at least 1.0 g/dL at any time between baseline and the end of study (day 56) or time of intervention. The efficacy data reviewed indicates that there was a significant (p-value 0.03) difference between Venofer treated group and oral iron treated group in the percentage of subjects with $\geq$ 1.0 g/dL hemoglobin increase from baseline. It is worth mentioning that the Cochran-Mantel-Haenszel test (which takes into account of EPO status) did not show a significant difference (p-value 0.16) between the Venofer treated group and oral iron treated group in the percentage of subjects with $\geq$1.0 g/dL hemoglobin increase from baseline. Thus the results are not robust.

Although the goals of current and the previous submissions were to study the effectiveness of Venofer in increasing hemoglobin for CRF patients without dialysis, the two submissions differ in

1) Primary endpoints
2) Treatment period
3) Dosing time intervals.

Thus the two studies are not identical. Although the current submission is a positive study, the original study failed to demonstrate superiority of Venofer over oral iron and thus it is not feasible to say that the current study is a supportive study for the original submission. In addition, a major secondary endpoint of this study, the change of hemoglobin from baseline to day 56/end of study (which is similar to the primary endpoint of the original submission), did not indicate any support for the superiority of Venofer over oral iron in increasing hemoglobin in the management of anemia in non-dialysis dependent (NDD) CKD patients.

Subgroup analyses by gender indicated that there was interaction (p-value 0.05) between the gender and the treatment groups. The proportion of subjects achieving ≥1.0 g/dL increase in hemoglobin from baseline was significantly greater (0.004) in the Venofer group compared to the oral iron group among the male patients. However, there was a numerical superiority of the Venofer group compared to the oral iron group in the percentage of subjects with ≥ 1.0 g/dL hemoglobin increase from baseline in female patients

Subgroup analyses by race indicated that there was no interaction between the race and treatment groups.

Subgroup analysis by age-group indicated that there was a mild interaction (p-value 0.12) between the age-group (age-group < 65 and age-group ≥ 65) and treatment groups. The proportion of subjects achieving ≥1.0 g/dL increase in hemoglobin from baseline was significantly greater (0.006) in the Venofer group compared to the oral iron group in the age-group ≥ 65. Moreover, there was a numerical superiority of the Venofer group compared to the oral iron group in the percent of subjects with ≥ 1.0 g/dL hemoglobin increase from baseline.

Subgroup analyses by center (pooled) indicated that there was no interaction between the center (pooled) and treatment groups.

The overall incidence of treatment-emergent adverse events was generally similar between the Venofer (70%) and oral iron (65%) groups.

2. *INTRODCTION*

2.1 *Overview*

Venofer is indicated in the treatment of iron deficiency anemia in chronic renal failure patients (CRF) undergoing chronic hemodialysis and receiving supplemental erythropoietin therapy. It was originally approved on the basis of 100 mg of iron sucrose injection given over 5 minutes per dialysis session and up to a total dose of 1,000 mg for each treatment cycle.

In this submission, the sponsor submitted a single protocol (Protocol 1VEN99027) which compared the efficacy and safety of Venofer (intravenous iron sucrose) over oral iron for subjects who were anemic and had been diagnosed with Chronic Renal Failure but are not on dialysis. Patients over 18 years of age, diagnosed with renal insufficiency and anemia, were eligible. Patients were randomized to either Venofer or oral $FeSO_4$, t. i. d.

2.2 **Data Sources**

This submission provided a single study to demonstrate that the efficacy and safety data is in support of the intravenous use of Venofer (iron sucrose injection) 1000 mg in a divided dose of over a 14-day period (either 500 mg infusion on days 0 and 14 or 200 mg injection on five different occasions within the 14-day period) in CRF patients who are not on dialysis. The reviewed documents were paper submission, and the data from these studies were archived in the FDA internal electronic document room under network path \\CDSESUB1\N21135\S_008\2005-04-11.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Applicants Results and Conclusions

The sponsor concluded that a statistically significant larger proportion of Venofer subjects had an increase in hemoglobin $\geq$ 1.0 g/dl (35/79; 44%) compared to oral iron subjects (23/82; 28%) during the study.

The overall incidence of treatment-emergent adverse events was generally similar between the Venofer (70%) and oral iron (65%) groups except for the incidence of gastro-intestinal disorders (9% Venofer and 18% oral iron).

3.1.2 Statistical Methodologies

The primary measure of efficacy compared the proportion of subjects with increase in hemoglobin of at least 1.0 g/dL at any time between baseline and the end of study or time of intervention.

The primary analysis of the primary endpoint was the unstratified comparison of the hemoglobin response rate between the two study arms (Venofer versus oral iron) in the combined non-erythropoietin and erythropoietin population, using a 2-sided Fisher's exact test at the 0.05 significance level. The primary efficacy endpoint was summarized for the Intent-to-Treat population. Analysis of covariance (ANCOVA) was used to evaluate the changes in hemoglobin and ferritin level from baseline to day 43 and day 56.

Patients who dropped out of the study were included in the analysis up to the time point when the patient is withdrawn.

A logistic regression model was used to evaluate the effect of potential covariates on the odds ratio of achieving the 1.0 g/dL hemoglobin response at day 56 visit based on the last observation carried forward method. The covariates to be evaluated included, but were not limited to, baseline hemoglobin, baseline ferritn, center, age-group, gender, race, interaction between treatment effects and each of the covariates. Odds ratios based on the final model were removed if their effects were not statistically significant.

3.1.3 Detailed Review

In order to support the safety and efficacy of Venofer, the sponsor conducted an active controlled study (1VEN030027) to compare efficacy and safety of Venofer (either 500 mg infusion on days 0 and 14 or 200 mg injection on five different occasions within the 14-day period) with respect to oral iron 325 mg three times daily for 56 days plus epoetin for managing anemia in patients with CRF not receiving dialysis. There is a single primary endpoint in this study: an increase of hemoglobin of at least 1.0 g/dL at any time between baseline to end of study (day 56).

Study design:

This was an open–label, Phase III, randomized, active control study. Anemic non-dialysis dependent chronic kidney disease (NDD-CKD) subjects with a diagnosis of renal insufficiency, who required iron supplementation, met all inclusion/exclusion criteria, and had given informed consent were enrolled. The duration of the study for each subject was a maximum of 18 weeks. Subjects were screened for study entrance eligibility and then followed an enrollment phase for a maximum of 10 weeks. Once subjects met the criteria for randomization (described later), they were randomized into the study.

At randomization, subjects were stratified by gender, hemoglobin levels (≤ 9.0 g/dL, 9.1 – 10.0 g/dL, 10.1 – 11.0 g/dL), and erythropoietin use. Subjects were randomly assigned to either Venofer (500 mg IV infusion administered over 3.5-4 hours on days 0 and 14 or 200 mg injections administered over 2-5 minutes on five different occasions from day 0 to day 14) or ferrous sulfate (325 mg Po TID x 56 days). The sponsor did not mention why two different modes (500 mg or 200 mg) of dosing of Venofer were administered. The erythropoietin dose was to remain fixed for dosage reductions because of safety reasons. Assessments for efficacy (complete blood count) and iron indices) and safety (adverse events) were performed every 2 weeks following the first dose of the drug through day 56. The quality-of-life assessment was performed at day 0 and day 56.

Inclusion Criteria:

Male or female subjects >18 years of age, with a diagnosis of renal insufficiency, hemoglobin ≤11.5 g/dL, and renal anemia were included in the study.

1) Hemoglobin ≤ 1.0 g/dL based on the average of 2 laboratory value drawn on different days within a 7-day period;

2) The difference between the 3 laboratory values could not exceed 0.5 g /dL';

3) TSAT ≤25%; ferritin ≤300 ng/mL; stable or no erythropoietin use for 8 weeks; no iron following enrollment, continued to meet all non-laboratory inclusion /exclusion criteria.

Methods for Assigning Subjects to a Treatment:

All eligible subjects were stratified by gender and hemoglobin level (≤ 9.0 g/dL versus 9.1 to 10.0 g/dL versus 10.1 to 11.0 g/dL), independent of the erythropoietin-treated and non-erythropoietin treated subgroups. Within each combination of strata, subjects were randomized in 1:1 ratio to iron Group (A) and Venofer Group (B)

Patients' disposition:

The following table shows subject disposition including the number of subjects in each treatment group who were planned, randomized, treated and evaluated for safety.

Table 1: Patients' Disposition

Number of Subjects	Ferrous Sulfate 325 mg/3 times daily x 56 days	Venofer 1000 mg/within 14-day period
Planned	80	80
Randomized	93	95
Treated and Evaluated for Safety	91	91

Sample Size Estimation:

The sample size for this study was based on the hypothesis that the response rate with a 1.0 g/dL increase in hemoglobin over pretreatment levels was 40% in the iron sucrose arm and 15% in the oral iron arm. A minimum of 72 subjects was required in each arm to assess such a difference in response by means of Fisher's exact test with a 2-sided significance level 0.05 and power of 0.90.

Efficacy Assessments:

The primary efficacy measure was comparisons of the proportion of subjects with an increase in hemoglobin of at least 1.0 g/dl at any time between baseline and the end of the study termination.

The secondary measures of efficacy are:

1. The "clinical response" rate between the two treatment groups in the combined non-erythropoietin and erythropoietin treated population, defined as an increase in ferritn of at least 160 ng/mL anytime between baseline and the end of the study or time of termination. The changes in hemoglobin and ferritin were not required to be simultaneous.

2. The proportion of subjects with an increase in hemoglobin of at least 1.0 g/dL between baseline and end of the study or time of intervention in erythropoietin versus non-erythropoietin treated subjects.

3. The proportion of subjects with an increase in hemoglobin of at least 1.0 g/dL between baseline and end of study or time of intervention in subjects with baseline ferritin < 100 ng /mL.

4. Clinical response in subjects with baseline ferritin <100 ng/mL

Statistical Analyses:

The primary measure of efficacy compared the proportion of subjects with increase hemoglobin of at least 1.0 g/dL at any time between baseline and the end of study or time of intervention.

The primary analysis of the primary endpoint was the un-stratified comparison of the hemoglobin response rate between the 2-study arms (Venofer versus oral iron) in the combined non-erythropoietin and erythropoietin population, using a 2-sided Fisher's exact test at the 0.05 significance level.

Safety:

Adverse events and serious adverse events.

Demographic and Baseline Characteristics:

Demographic Characteristics:

The following table summarizes the demographic characteristics of the patient population.

Table 2: Patients' Demographic Characteristics

Demographic characteristics	Venofer (N=91)	Oral Iron (N=91)
Age (years)		
Age <65	49 (54%)	43 (47%)
Age>65	42 (46%)	48 (53%)
Gender		
Male	29 (32%)	27(30%)
Female	62 (68%)	64 (70%)
Race:		
Black	31 (34%)	40 (44%)
Caucasian	55 (60%)	46 (51%)
Other (Asian/Hispanic)	5 (6%)	5 (6%)
Weight (kg)		
Mean (sd)	84.9 (23%)	84.6 (24)

The sponsor reported that there were no statistically significant differences between the two treatment groups for any of the demographic or baseline characteristics. It can be seen from the above table that the majority of the subjects in both treatment groups were female (68% in Venofer group and 70% in oral iron) group). Both treatment groups had a majority of Caucasians (60% in Venofer and 51% in oral iron).

Baseline Characteristics

The following table summarizes the baseline characteristics of the patient population:

Table 3: Patients' Baseline Characteristics

Baseline characteristics	Venofer (91)	Oral iron (N=91)
Erythropoietin Status		
EPO user	41(45%)	39(43%)
Non-EPO user	50 (55%)	52(57%)
Baseline Hemoglobin (g/dL)	10.2 (0.65)	10.1 (0.71)
Baseline TSAT (%)		
Mean (sd)	16.3 (5.3)	16.7 (5.02)
Baseline Ferritin(ng/mL)		
Mean (sd)	91.0(70.64)	100.6 (73.66)
Baseline TSAT<20% and ferritin < 100 ng/mL	35 (39%)	38 (42%)
Baseline Creatine Clearance	29.5 (14.93)	29.2 (20.55)
Prior Iron Intolerance		
Yes	3(3%)	3(3%)
Oral iron	2 (2%0	2 (2%)
Other	1(1%)	1(1%)

The sponsor reported that there were no statistically significant differences between the two treatment groups in the Intent-to-Treat Population for any of the baseline characteristics. However, a great proportion of subjects in the oral iron group (68%) had a baseline creatine clearance $\leq$ 30 mL/min/1.73 m^2 compared to subjects in the Venofer group.

Data Sets Analyzed:

All subjects (N=182) who received at least one dose of Venofer or oral iron were included in the safety population. Seventy-nine subjects in the Venofer group and 82 subjects in the oral iron group were included in the Intent-to-Treat Population. Twelve (12) subjects in the Venofer group were excluded from the Intent-to-Treat Population due

to no post-baseline efficacy data (4 subjects) or had unstable use of erythropoietin during the 8 weeks prior to randomization (8 subjects). Nine subjects in the oral iron group were excluded from the Intent-to-Treat population due to no post-baseline efficacy data (1 subject) or had unstable use of erythropoietin during the 8 weeks prior to randomization (8 subjects). A summary of the datasets is presented in the following Table:

Table 4: Datasets Analyzed

Population	Venofer (N=91)	Oral Iron (N=91)
Subjects Treated	91 (100%)	91 (100%)
Safety Population	91 (100%)	91 (100%)
Intent-to-Treat Population	79 (87%)	82 (90%)

Efficacy analyses:

A summary of the proportion of subjects with an increase in hemoglobin $\geq$ 1.0 g/dL during the study is summarized in the following table.

Table 5: Summary of the Proportion of Subjects with $\geq$ 1.0 g/dL Increase From Baseline in Hemoglobin during the Study (Intent-to-Treat Population).

	Venofer (N=79)	Oral Iron (N=82)	Fisher's exact test p-value
Anytime during the study	35 (44%)	23 (28%)	0.03

It can be seen that from the above table that Venofer (200 mg injection on five different occasions during a 14-day period or 500 mg infusion on days 0 and 14) was significantly more effective (p-value 0.03) in the management of anemia in NDD-CKD patients. As a single study, the evidence from this study is not statistically persuasive. It is to be noted here that the estimated success rate (28%) for the oral iron group is much higher than the expected success rate (15%).

Secondary Analysis:

Logistic Regression Analysis

The sponsor conducted logistic regression analysis of the primary endpoint. A summary of the final logistic regression model for the odds of achieving ≥ 1.0 g/dL increase from baseline in hemoglobin during the study is presented in the following table:

Table 6: Summary of the Final Logistic Regression Model (Intent-to-Treat Population)

Variable	Odds Ratio		P-value
	Estimate	95% CI	
Treatment group	2.0	1.01, 3.83	0.05

Logistic regression analysis indicated Venofer statistically significantly increased the odds of achieving ≥ 1.0 g/dL increase from baseline in hemoglobin compared to oral iron.

Secondary Efficacy Endpoints:

Clinical Response:

Clinical response was defined as an increase in hemoglobin ≥1.0 g/dL and an increase in ferrtin ≥ 160 ng/mL anytime between baseline and the end of study or time to intervention.

A summary of the proportion of subjects with a clinical response during the study is presented in the following table:

Table 7: Summary of the Proportion of Subjects with a Clinical Response During the Study(Intent-to-Treat Population)

	Treatment group		Fisher's exact test's p-value
	Venofer (N=79)	Oral iron (N=82)	
Anytime during the study	31 (39%)	1 (1%)	<0.0001

It can be seen from the above table that a statistically significantly greater proportion of Venofer subjects (31/79; 39%) compared to oral iron subjects (1/82; 1%) had a clinical response during the study. Note that clinical response is a not a useful endpoint since the response rate in the oral iron group is low relative to the primary endpoint rate.

Mean changes from baseline in Hemoglobin over time:

The following table summarizes the efficacy results based on changes of hemoglobin from baseline to Day 42 and Day 56/end of the study.

Table 8: Summary of the Proportion of Subjects with a Clinical Response during the Study (Intent-to-Treat Population)

	Mean Change		Difference (95% CI)	ANCOVA P-value
	Venofer	Oral Iron		
Day 42				
N	64	65		
Least Squares means*	0.69	0.37	0.31 (0.02, 0.61)	0.04
Day 56/End of the Study				
N	72	71		
Least Square means*	0.64	0.37	0.28 (-0.02, 0.58)	0.06

Note: Baseline Creatinine Clearance as a covariate; *: Least Squares means were calculated from ANCOVA using baseline creatinine as a covariate.

A statistically significant larger mean increase from baseline to day 42 in hemoglobin was observed for the Venofer group compared to the oral iron group. However, there was no statistically significant difference between the treatment groups at Day 56/end-of-study. Note that the secondary endpoint 'change of hemoglobin from baseline to Day 56/end of the study' is similar to the primary endpoint of the original submission. Thus, this study does not adequately support the original study.

3.2 Evaluation of Safety

There were no statistical tests involved in assessing the significance of the safety parameters.

Adverse Events:

All analyses were performed using the safety population defined as all subjects who received at least one dose of study drug.

The overall incidence of treatment-emergent adverse events was generally similar between the Venofer (70%) and oral iron (65%) groups. The sponsor reported that the most commonly (≥ 5% of the subjects in either group) experienced treatment-emergent adverse events in the Venofer group were dysgeusia (8), peripheral edema (8%), constipation (6%), diarrhea NOS (6%), dizziness (6%), hypertension NOS (6%), and nausea (6%). The most commonly experienced treatment-emergent adverse events in the oral iron group were constipation (12%), diarrhea NOS (10%), nausea (10%), edema NOS (9%), fatigue (7%), vomiting NOS (7%), urinary tract infection NOS (7%), and fecal occult blood positive (6%).

The majority of the treatment-emergent adverse events experienced during the study were considered by the investigator to be Grade 1 or 2 in intensity. The sponsor reported that during the study, at least 1 drug-related treatment emergent adverse events was experienced by 23% (21/91) of the subjects in the Venofer group and 19% (17/91) of the subjects in the oral iron group.

The sponsor mentioned that the most notable differences between the treatment groups in drug related treatment emergent adverse events was for the incidence of gastro-intestinal disorders (9% Venofer and 18% oral iron). The Venofer group had a higher incidence of dysgeusia (6%), characterized as abnormal taste sensation, compared to the oral iron group (0%); whereas, the oral iron group had a higher incidence of constipation (9%), diarrhea (3%) and nausea (3%) compared with the Venofer group (1%, 0%, and 1%, respectively).

The sponsor reported that no clinically important trends were observed when t treatment-emergent adverse vents were summarized according to age, gender, race, or dose.

Serious Adverse Events:

The were no deaths during the study. Ten (1%) subjects in the Venofer group and 6 (7%) subjects in the oral iron group experienced serious adverse events. One subject in the Venofer treatment group (500 mg) reported serious adverse events of dyspnea and hypotension NOS during the study that were considered by investigator to be related to the study drug. Three (3, 3%) subject in the Venofer group and 2 (2%) subjects in the oral iron group prematurely discontinued from the study due to the occurrence of adverse events. The adverse events leading to premature discontinuation in the 3 Venofer subjects were all considered study drug related (hypotension,NOS, dyspnea, and nausea). Two of the Venofer subjects experienced Grade 3 hypotension soon after dosing (500 mg) that were considered by the investigator to be probably related to study drug. Both of these subjects weighted < 70 kg (62.5 kg and 46.2 kg, respectively) and both prematurely discontinued due to these events.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The sponsor did not conduct tests for interactions between subgroups and the treatments analyses. This reviewer examined treatment response for homogeneity among the following subgroups:

Male versus Female:

Race (Caucasian versus Black and Other)

Age < 65 years versus >= 65 years;

Sub-group analyses are summarized below. Note that these subgroup analyses were not adjusted for multiplicity. The comparisons within each subgroup are based small samples. These comparisons are between two non-randomized arms. Thus the results have to be interpreted carefully.

Gender

This reviewer conducted the treatment by gender interaction test using Breslow-Day test. The test detected an interaction (p-value 0.05) between gender and the treatment-group.

The response rate by gender is summarized in the following table:

Table 9: Summary of Number (%) of Subjects with ≥ 1 g/dL Increase From Baseline by Gender (Intent-to-Treat Population)

Gender	Treatment group	
	Venofer	Oral iron
Male	14/26 (54%)	4/26 (15%)
Female	22/53 (42%)	19/56 (34%)

The proportion of subjects achieving ≥1.0 g/dL increase in hemoglobin from baseline was significantly greater (0.004) in the Venofer group compared to the oral iron group among the male patients. However, there was a numerical superiority of the Venofer group compared to the oral iron group in the percentage of subjects with ≥ 1.0 g/dL hemoglobin increase from baseline in female patients

Race

This reviewer conducted the treatment by race interaction test using Breslow-Day test. The test failed to detect an interaction (p-value 0.76) between gender and the treatment-group. The response rate by race is summarized in the following table:

Table 10: Summary of Number (%) of Subjects with ≥ 1g/dL Increase From Baseline by Race(Intent-to-Treat Population)

Race	Treatment group		P-value
	Venofer	Oral iron	
Caucasians	20/44 (46%)	14/40 (35%)	0.33
Black	11/30 (37%)	7/38 (18%)	0.09
Others	4/5 (80%)	2/4 (50%)	0.34

It can be seen from the above table that there was a numerical superiority of the Venofer group compared to the oral iron group in the percent of subjects with ≥ 1.0 g/dL hemoglobin increase from baseline in all races.

Age-group:

This reviewer conducted the Breslow-Day test for interaction between age-group and the treatments. The test showed that there was a mild interaction (p-value 0.12) between age-group and the treatments. The response rate by age-group is summarized in the following table:

Table 11: Summary of Number (%) of Subjects with ≥ 1 g/dL Increase From Baseline by Age-group(Intent-to-Treat Population)

Age-group	Treatment group	
	Venofer	Oral iron
Age < 65	15/41 (37%)	13/39 (33%)
Age ≥ 65	20/38 (53%)	10/43 (23%)

The proportion of subjects achieving ≥1.0 g/dL increase in hemoglobin from baseline was significantly greater (0.006) in the Venofer group compared to the oral iron group in the age-group ≥ 65. Moreover, there was a numerical superiority of the Venofer group compared to the oral iron group in the percent of subjects with ≥ 1.0 g/dL hemoglobin increase from baseline.

4.2 Other Special /Subgroup Populations

In this section, we describe analyses by Erythropoietin (EPO) status and by center.

EPO Status

The sponsor did not conduct tests for interactions between EPO status and the treatments. This reviewer examined homogeneity of treatment response between EPO users and non-EPO users. This reviewer conducted the Breslow-Day test for interaction between EPO status and the treatments. The test failed to show interaction (p-value 0.69) between EPO-status group and the treatments. The response rate by EPO status is summarized in the following table:

Table 12: Summary of Number (%) of Subjects with ≥ 1 g/dL Increase From Baseline by EPO Status (Intent-to-Treat Population)

EPO Status	Treatment group	
	Venofer	Oral iron
EPO Users	18/47 (38%)	13/51 (26%)
Non-EPO Users	17/32 (53%)	10/31 (32%)

It can be seen from the above table that there was a numerical advantage of the Venofer group compared to the oral iron group in the percent of subjects with ≥1.0 g/dL hemoglobin increase from baseline in both EPO and non-EPO users.

The Cochran-Mantel-Haenszel test (adjusting for EPO status) did not show a significant difference (p-value 0.16) between the Venofer treated group and oral iron treated group in the percent of subjects with ≥1.0 g/dL hemoglobin increase from baseline. Note that the Cochran-Mantel-Haenszel strategy potentially removes the confounding influence of the EPO status that comprise the stratification (EPO users and non-EPO users) and so provides a gain in power for detecting association by comparing like subjects with like subjects. Note that the CMH test loses power when the subjects within each stratum are not homogeneous. Note that at randomization, the subjects were stratified by gender, hemoglobin levels at baseline and EPO use. Thus, it is possible that the patients within ether block (EPO Status/ non-EPO status) might not be homogeneous.

Center

The sponsor did not conduct tests for interactions between the centers and the treatments. The reviewer conducted a test for treatment by center (pooled) interaction. The Breslow-Day failed (p-value 0.35) to detect any interaction between the centers and the treatments. The response rate by EPO status is summarized in the following table:

Table 13: Summary of Number (%) of Subjects with ≥ 1 g/dL Increase From Baseline by Center (Intent-to-Treat Population)

Center #	Treatment group	
	Venofer	Oral iron
Center 001	3/9 (33%)	1/11 (9%)
Center 002	7/11 (64%)	2/7 (29%)
Center 003	2/6 (33%)	3/7 (43%)
Center 004	1/7 (14%)	2/11 (18%)
Center 005	2/8 (25%)	1/5 (20%)
Center 006	5/6 (83%)	1/5 (20%)
Center 007	2/7 (29%)	1/8 (3%)
Center 008	4/7 (57%)	4/8 (50%)
Center 009	5/10 (50%)	5/6 (83%)
Center 010	4/8 (50%)	3/14 (21%)

It can be seen from the above table that there was a numerical superiority of the Venofer group compared to the oral iron group in the percent of subjects with ≥1.0 g/dL hemoglobin increase from baseline in all the centers except centers 003, 004 and 009. It is difficult to interpret the results of centers 003, 004 and 009 because of small sample sizes in those centers.

5. SUMMARY AND CONCLUSIONS

5.1 **Statistical Issues and Collective Evidence**

The current NDA follows an earlier submission for Venofer for the same indication (the use of Venofer in the treatment of iron deficiency anemia for chronic renal failure patients who are not on dialysis) which received a non-approval letter in June, 2004. In this subsection, this reviewer describes the original submission as well as its relation to the current submission.

Original submission:

Objective:

The objective of this study was to lend support to the intra-venous use of Venofer (iron sucrose injection) 200 g/dL (given on Days 1, 8, 15, 22 and 29) in CRF patients who are not on dialysis.

Brief summary of the trial:

Study 1VEN99012 was an open label, randomized, multi-center, active controlled, phase II/III study. Anemic patients with CRF not receiving dialysis who required iron supplementation, met all of the inclusion criteria, and had given informed consent were enrolled. Patients were on study approximately 5 months. Screening of patients was performed and eligibility data were collected over 2 weeks, followed by 29 days of drug treatment and end-of-treatment evaluation on day 43 (Treatment Phase). Each patient received either ferrous sulfate (325 mg orally three times a day on days 1 to 29) or Venofer (200 mg intravenous injection on days1, 8, 15, 22, and 29).

Efficacy assessments included hematological parameters measured on days 15, 36, 43, and every 2 weeks thereafter and iron indices measured on days 36, 43, 57, 86, and 114. Safety assessments included recording of adverse events, physical examinations, vital signs, ECG and clinical laboratory test.

A total of 96 patients (48 oral and 48 Venofer) received at least 1 or more doses of study medication. Forty-four (44; 92%) of the 48 patients in the oral group and 39 (81%) of the 48 patients in the Venofer group completed the treatment phase.

All patients received epoetin 2000 U subcutaneously weekly on treatment visit days. Dose reduction was only to be performed if hemoglobin was > 12.5 g/dL or if the hemoglobin increase exceeded 2.6 g/dL an any 1-month period.

The following table summarizes efficacy results for both hemoglobin and serum ferritin.

Table 14: Summary of Mean Changes from Baseline Hemoglobin to Day 43 during the Treatment Phase(Intent-to-Treat Population)

Oral iron (N=48)			Venofer (N=48)			ANCOVA P-value LS [1] mean difference (Venofer – oral) (95% CI)
Baseline	Change from baseline	p-value	Baseline	Change from Baseline	p-value	
9.7	0.7	<0.0001	9.9	1.0	<0.0001	0.14[2] 0.3 (-.01, 0.7)

1: LS (Least Squares)
2: Treatment, Baseline Ferritn, EPO status, and Race * Treatment in the model
3: Treatment, Baseline Ferritin, and Baseline Ferritin * Treatment in the model

It can be seen from the above table that Venofer was not significantly different from oral iron in increasing hemoglobin for CRF patients not on hemodialysis.

Conclusions

The evidence from this single study reviewed does not indicate support for the safety of and efficacy of Venofer in increasing hemoglobin for CRF patients not on hemodialysis when compared with oral iron. Although the data reviewed indicates the superiority of Venofer in increasing serum ferritin for CRF patients not on hemodialysis when compared with oral iron, the control group did not have any improvement at all in serum ferritin which contributed to the significant difference between the two treated groups. In fact, there was a negative change (-5.1) of serum ferritin from baseline. As a result, this single study cannot be taken as a basis of approval of 200 mg iron for CRF patients who are not on dialysis.

Current Submission:

In its review of the original submission, the FDA noted that erythropoietin was initiated concurrently with iron in majority of the subjects. Any effect of iron may have been confounded by the concomitant initiation of erythropoietin.

This current submission (NDA 21-135/SE1-008/AZ; 2nd review cycle) was designed by Luitpold Pharmaceutical, Inc., to distinguish iron effects from those of erythropoietin by requiring stable erythropoietin for a prolonged period prior to randomization and to evaluate the potential role of the intravenous iron in both the erythropoietin and non-erythropoietin treated populations. Note that this study was planned before the sponsor received the non-approval letter in June 2004. This submission addresses the efficacy and safety data in support of the intra-venous use of Venofer (iron sucrose injection) 1000 mg in divided dose of over a 14-day period (either 500 mg infusion on days 0 and 14 or 200 mg injection on five different occasions within the 14-day period) in chronic renal failure (CRF) patients who are not on dialysis.

Although the goals of current and the previous submissions were to study the effectiveness of Venofer in increasing hemoglobin for CRF patients without dialysis, the two submissions differ in

1) Primary endpoints
2) Treatment period
3) Dosing time intervals.

Thus the two studies are not identical. Because the current submission is a positive study and the original study was a negative study, it is not feasible to say that the current study is a supportive study for the original submission. On the other hand, the current submission does not provide statistically persuasive results (p-value 0.03 by primary analysis; p-value 0.05 by secondary analysis) when considered as a single study. The Cochran-Mantel-Haenszel test (adjusting for EPO status) did not show significant difference (p-value 0.16) between the Venofer treated group and oral iron treated group in the percentage of subjects with $\geq$1.0 g/dL hemoglobin increase from baseline. In addition, a major secondary endpoint of this study, the change of hemoglobin from baseline to day 56/end of study (which is similar to the primary endpoint of the original submission), did not indicate any support for the superiority of Venofer over oral iron in increasing hemoglobin in the management of anemia in non-dialysis dependent (NDD) CKD patients.

This is an active control study with oral iron as a comparator. The oral iron has an effect of increasing hemoglobin in general. The medical review should address this issue in depth.

5.2 CONCLUSIONS AND RECOMMENDATIONS

Efficacy:

The efficacy data from the current submission indicates that Venofer (200 mg injection on five different occasions during a 14-day period or 500 mg infusion on days 0 and 14) was significantly more effective (p-value 0.03) in the management of anemia in NDD-CKD patients. It is worth mentioning the Cochran-Mantel-Haenszel test (after adjusting for EPO status) did not show significant difference (p-value 0.16) between the Venofer treated group and oral iron treated group in the percent of subjects with $\geq$1.0 g/dL hemoglobin increase from baseline.

A major secondary endpoint (change of hemoglobin from baseline to day 56/end of study) of this study (which is similar to the primary endpoint of the original submission) did not indicate a support for the superiority of Venofer over oral iron in increasing hemoglobin in the management of anemia NDD-CKD patients.

Although the goals of current and the previous submissions were to study the effective ness of Venofer in increasing hemoglobin for CRF patients without dialysis, the two submissions differ in

1) Primary endpoints
2) Treatment period
3) Dosing time intervals.

Thus the two studies are not identical. Because the current submission is a positive study and the original study was a negative study, it is not feasible to say that the current study is a supportive study for the original submission. On the other hand, the current submission does not provide statistically persuasive results (p-value 0.03 by primary analysis; p-value 0.05 by secondary analysis) when considered as a single study. In addition, a major secondary endpoint of this study, the change of hemoglobin from baseline to day 56/end of study (which is similar to the primary endpoint of the original submission), did not indicate any support for the superiority of Venofer over oral iron in increasing hemoglobin in the management of anemia in non-dialysis dependent (NDD) CKD patients. However, this is an active control study with oral iron as a comparator. The oral iron has an effect of increasing hemoglobin in general. The medical review should address this issue in depth.

Safety:

In the current submission, the incidence of any specific treatment related adverse events was comparable between the two groups except the incidence of gastro-intestinal disorders (9% Venofer and 18% oral iron).

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Mushfiqur Rashid
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-135/S-008

Drug Name: Venofer (iron sucrose injection)

Indication(s): Ttreatment of iron deficiency anemia in chronic renal failure patients who are not on dialysis

Applicant: Luitpold Pharmaceuticals, Inc.

Date(s): Submitted August 18, 2003; PDUFA goal date June 18, 2004

Review Priority: Standard

Biometrics Division: Division of Biometrics II (HFD-715)

Statistical Reviewer: Mushfiqur Rashid, Ph.D.

Concurring Reviewers: Stella Grosser, Ph.D.

Medical Division: Gastro-Intestinal and Coagulation Drug Products (HFD-180)

Clinical Team: Min Lu, M.D., M.P.H.

Project Manager: Tanya Clayton

Keywords: NDA review, clinical studies, safety studies, ANCOVA

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Venofer is indicated in the treatment of iron deficiency anemia in chronic renal failure patients (CRF) undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy. It was originally approved on the basis of 100 mg of iron sucrose injection given over 5 minutes per dialysis session and up to a total dose of 1,000 mg for each treatment cycle. This submission addresses the efficacy and safety data in support of the intra-venous use of Venofer (iron sucrose injection) 200 mg (given on Days 1, 8, 15, 22 and 29) in chronic renal failure (CRF) patients who are not on dialysis.

In order to support the safety and efficacy of Venofer, the applicant conducted an active controlled study (1VEN99012) to compare efficacy and safety of Venofer 200 mg with respect to oral iron 325 mg daily on days 1 through 29 plus epoetin for managing anemia in patients with CRF not receiving dialysis. There are two primary endpoints in this study: Change of hemoglobin from baseline to end of study (day 43) and Change of serum ferritin from baseline to end of study.

The evidence from this single study reviewed does not support the safety and efficacy of Venofer in increasing hemogolobin for CRF patients not on hemodialysis when compared with oral iron. Although the data reviewed indicates the superiority of Venofer in increasing serum ferritin for CRF patients not on hemodialysis when compared with oral iron, the control group did not have improvement at all in serum ferritin. It appears that the failure of the control group to improve serum ferritin at Day 43 contributed to the significant difference between the two treated groups. In fact, there was a negative change (-5.1) of serum ferritin from baseline with a standard deviation of 36.81. As a result, this single study cannot be taken as a basis of approval of 200 mg iron for CRF patients who are not on dialysis.

The incidence of any specific treatment related adverse events were comparable between the two groups.

In order to receive an approval for Venofer 200 mg, the applicant is suggested to conduct another trial with CRF patients without dialysis. The applicant may consider placebo controlled trial or adding a placebo arm along with an oral iron treated arm in the new trial.

1.2 Brief Overview of Clinical Studies

Venofer (iron sucrose injection) is a complex of polynuclear iron (III)-hydroxide in sucrose. It is approved for use in replenishing iron in patients receiving erythropoetin (a hormone that stimulates red blood cell production) and undergoing chronic hemodialysis, which involves filtering the blood in order to remove waste products. In these patients, an iron deficiency is caused by blood loss during the dialysis procedure, increased erythropoiesis (red blood cell production), and insufficient absorption of iron from the gastrointestinal tract. Iron is essential for the synthesis of hemoglobin, which is responsible for the transport of oxygen throughout the body.

The drug has been approved and marketed in over 63 countries worldwide since 1950. The original recommended dosing regimen for Venofer is 100 mg over 5 minutes by the intravenous push administered up to three times per week for the treatment of iron deficiency patients under dialysis. The current submission is for CRF patients without dialysis. Also the approved dosing regimen (100 mg) is different from the proposed dosing regimen in the current submission (200 mg).

Study design:

Study 1VEN99012 was an open label, randomized, multi-center, active controlled, phase II/III study. Anemic patients with CRF, not receiving dialysis, who required iron supplementation and who met all of the inclusion criteria and had given informed consent were enrolled. Patients were on study approximately 5 months. Screening of patients was performed and eligibility data were collected over 2 weeks, followed by 29 days of drug treatment and end-of-treatment evaluation on Day 43 (Treatment Phase). Each patient received either ferrous sulfate (325 mg orally three times a day on days 1 to 29) or Venofer (200 mg intravenous injection on days1, 8, 15, 22, and 29).

Efficacy assessments included hematologic parameters measured on days 15, 36, 43, and every 2 weeks thereafter and iron indices measured on days 36, 43, 57, 86, and 114. Safety assessments included recording of adverse events, physical examinations, vital signs, ECG and clinical laboratory test. The primary efficacy endpoints of the study were changes in hemoglobin and serum ferritin from baseline to Day 43 (end of treatment).

A total of 96 patients (48 oral and 48 Venofer) received at least 1 or more doses of study medication. Forty-four (44; 92%) of the 48 patients in the oral group and 39 (81%) of the 48 patients in the Venofer group completed the treatment phase.

All patients received epoetin 2000 U subcutaneously weekly on treatment visit days. Dose reduction was only to be performed if hemoglobin was > 12.5 g/dL or if the hemoglobin increase exceeded 2.6 g/dL an any 1-month period.

1.3 Statistical Issues and Findings

The null hypotheses of interest were that there was no difference in hemoglobin and ferritin change from baseline to Day 43 between oral iron and intravenous iron sucrose. The alternative hypotheses were that there was a difference between the 2 treatment groups in these parameters. Hence, all inferential analyses were made using a two-sided test.

Analysis of covariance (ANCOVA) was used to evaluate the changes in hemogobin and ferritin level from baseline to Day 43. A paired sample t-test was used to evaluate from change from baseline within each treatment group at each visit. As a post-hoc analysis, Multivariate Analysis of Variance (MANOVA) (considering the percent change from baseline to Day 43 in hemoglobin and ferritin values as 2 dependent variables and treatment as the factor in the model) was performed.

An adjustment to multiplicity is carried using Hochberg (1988) procedure. Since there were two primary null hypotheses tested independently in this study, the Hochberg (step-up) method was used to control the overall alpha to be 0.05. Based on this method, if the least significant p-value (say p2) was less than or equal to the significance level of 0.05, both hypotheses of interest were rejected; other wise, p2 was retained and the other p-value, was compared with the significance level of 0.025.

The objective of this study was to support of the intra-venous use of Venofer (iron sucrose injection) 200 g/dL(given on Days 1, 8, 15, 22 and 29) in chronic renal failure (CRF) patients who are not on dialysis. The evidence from this single study reviewed does not indicate support for the safety of and efficacy of Venofer in increasing hemogolobin for CRF patients not on hemodialysis when compared with oral iron . Although the data reviewed indicates the superiority of Venofer in increasing serum ferritin for CRF patients not on hemodialysis when compared with oral iron, the control group did not have any improvement at all in serum ferritin which contributed to the significant difference between the two treated groups. In fact, there was a negative change (-5.1) of serum ferritin from baseline. As a result, this single study cannot be taken as a basis of approval of 200 mg iron for CRF patients who are not on dialysis.

Subgroup analyses (age-group, gender, and race) of the two primary endpoints indicated that there were no interaction between the subgroups and treatment groups.

The safety data showed that during the treatment phase, the overall incidence of treatment emergent adverse events for the oral iron (90%) and Venofer (88%) were similar. Gastro-intestinal disorders were the most commonly experienced treatment-emergent adverse events in both treatment groups (48% oral iron and 35% Venofer). In particular, Venofer treated patients had more cardiac disorders (25% versus 17%) and hyperglycemia NOS (8% versus 4%) than the oral iron treated group. The safety data also showed that during the treatment phase, the percentage of patients experienced at least one drug related treatment-emergent adverse event experienced by the (23% in the Venofer treated group and 40% the oral iron treated group) were comparable. Gastro-intestinal disorders were the most commonly experienced drug related treatment-emergent adverse events in both treatment groups (35% oral iron and 13% Venofer).

2. INTRODUCTION

2.1 Overview

Venofer is indicated in the treatment of iron deficiency anemia in chronic renal failure patients (CRF) undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy. It was originally approved on the basis of 100 mg of iron sucrose injection given over 5 minutes per dialysis session and up to a total dose of 1,000 mg for each treatment cycle. This submission addresses the efficacy and safety data in support of the intra-venous use of Venofer (iron sucrose injection) 200 mg (given on Days 1, 8, 15, 22 and 29) in chronic renal failure (CRF) patients who are not on dialysis.

The label for Venofer (iron sucrose injection) approved by the FDA in November 2000 referenced three clinical trials that were conducted to assess the safety and efficacy of Venofer. Two of the three trials were conducted in the United States and the other trial was conducted in South Africa. In the two trials performed in the United States, a total of 100 patients received Venofer as a 100 mg dose over 5 minutes without a required test dose. Each patients received 10 doses over consecutive hemodialysis sessions for a total 1,000 mg. Similarly, the South African trial enrolled 131 patients who received 100 mg doses of Venofer infused up to 25 minutes in consecutive dialysis sessions until they reached an individually calculated total iron dose based on their base line hemoglobin level and body weight.

In this submission, the applicant submitted a single protocol (Protocol 1VEN99012) which compared the efficacy and safety of Venofer (intravenous iron sucrose) administered to subjects who were anemic and had been diagnosed with Chronic Renal Failure but are not on dialysis. Patients over 18 years of age, diagnosed with renal insufficiency and anemia, were eligible. Patients were randomized to either Venofer or oral FeSO4, t. i. d.

2.2 Data Sources

The applicant provided a single study to demonstrate the safety and efficacy of Venofer 200 mg for the indication of iron deficiency for CER patients without dialysis.
The applicant submitted three other studies from the original submission to support the current submission. These three studies were conducted and analyzed by Luitpold Pharmaceuticals, Inc. to evaluate the efficacy of Venofer in the treatment of anemic hemodialysis patients. Venofer was approved in the US in November 2000 based on the three clinical trials. These trials were conducted to assess the safety and effectiveness of Venofer for CRF patients on dialysis. Two trials were conducted in the United States and one was conducted in South Africa. However,

these studies were conducted for ESRD patients who were undergoing dialysis where as current submission is for CRF patients with out dialysis. In addition, the approved dosing regimen (100 mg) is different from the current submission (200 mg). Because the patient populations and dosing regimens are different in the current submission and the original submission, these three studies cannot be considered as supportive studies.

Additionally, three studies from literature (see Table 1) were submitted to further profile Venofer. These supportive studies investigated the use of Venofer for CRF patients without dialysis. Table 1 describes these studies briefly.

Table 1: Table of Studies

Study	Study design	Treatment arms	Primary measures of efficacy
Silverberg et al (1996)	Open –label prospective study	200 mg of elemental iron as Veno-Ferrum was given IV in 50 mL of normal saline over 2 hours. This dose was given monthly for 5 months. All patients also received slow release oral preparation (100 mg elemental iron per day)	Change in Hemoglobin
Silverberg et al. (2001)	Randomized prospective study	Venofer group A: 200 mg of elemental iron as Venofer was given IV in 150 mL of normal saline over 60 minutes. This dose was given weekly for 5 doses. The patients also received 2000 IU of EPO weekly for 5 doses. Group B: Same iron dose no EPO.	Change in hemoglobin
Stoves et al. (2001)	Randomized prospective study	Venofer 300 mg over 2 hours, repeated monthly.Epoetin at in initial dose of 2000 U twice weekly. Oral iron 200 mg tid. Epoetin at an initial dose of 2000 IU twice weekly	Hematologic and biochemical parameters.

The studies varied from the single trial in that they were conducted using different designs, different phases and dosage strengths, and /or defined the primary efficacy variable differently. Only one (Stoves et al. 2001) of these 3 studies cited from the literature is an active controlled (oral iron) study. However, Venofer dose level (300 mg) and oral iron dose level (200 mg) were different from the pivotal study. Due to these variations, this reviewer primarily focused his review on the pivotal study. These three studies (cited from the literature) do not adequately serve as supporting studies for the current submission.

The reviewed documents were paper submission, and the data from these studies were archived in the FDA internal electronic document room under network path \\CDSESUB1\N21135\S_008\2004-02-26.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Applicant's Results and Conclusions

The primary efficacy endpoints of the study were changes in hemoglobin and serum ferritin from baseline to Day 43 (end of treatment). The null hypotheses of interest was that there was no difference in hemoglobin and ferritin change from baseline to Day 43 between oral iron and intravenous iron sucrose.

The applicant reported that the difference between the treatment groups for the mean change from baseline to Day 43 in hemoglobin was not statistically significant. However, the difference between the treatment groups in mean change from baseline to Day 43 in ferritin was statistically significant (p-value <0.0001).

Although not specified in the protocol, a secondary endpoint of clinical success was described in the Statistical Analysis Plan. In the treatment phase, during which epoetin therapy was held constant, 30 (63%) of the 48 patients in the Venofer group achieved clinical success (≥0.8% g/dL change from baseline in the hemogolobin and ≥ 160 ng/mL change from baseline in ferritin at any timepoint during the treatment phase), while none of the patients in the oral iron group met the criteria for the clinical success. The clinical success endpoint is not meaningful because in the oral iron group there were no successes. If the oral iron treated group does not show any successes, it is understood that oral iron therapy is not beneficial to the patients in increasing both hemoglobin and serum ferritin. However, the efficacy results of this submission showed that the oral iron therapy is significantly beneficial in increasing hemoglobin from baseline to the day 43.

In addition, an analysis using the MANOVA option in the PROC GLM procedure, considering a percent changes from baseline to Day 43 in hemogobin and ferritin values as 2 dependent variables and treatment as the factor in the model, was performed. The results of this analysis indicated a statistically significant treatment effect (p-value < 0.0001) for the test statistic of Wilk's Lambda. The applicant claimed that the percent change from baseline to Day 43 for both hemeoglobin and ferrtin was statistically significant different between the Venofer and oral iron treatment groups.

The applicant concluded that the overall adverse event profile demonstrated both treatment groups were well tolerated. Gastro-intestinal (GI) side effects were the most commonly reported events in both treatment groups. The oral iron group experienced more GI side effects (48% versus 35%) than the Venofer treated group. However, the Venofer treated group experience more cardiac disorders (25% versus 17%) and hypoglycemia (8% versus 2%) than the oral iron treated group. With the exception of taste disturbance, the adverse events profile reported in this study was consistent with current Venofer labeling.

3.1.2 Statistical Methodologies

Analysis of covariance (ANCOVA) was used to evaluate the changes in hemoglobin and ferritin level from baseline to Day 43.

A paired sample t-test was used to evaluate from change from baseline within each treatment group at each visit.

As a post-hoc analysis, an analysis using the multivariate analysis of Variance (MANOVA) option of the PROC GLM procedure (considering the percent change from baseline to Day 43 in hemoglobin and ferritin values a 2 dependent variables and treatment as the factor in the model) was performed.

Patients who dropped out of the study was included in the analysis up to the time point when the patient is withdrawn. Missing data were not be imputed unless otherwise specified for a specific parameter. Missing values were imputed from the previous time point.

The applicant mentioned in the protocol that covariates (e.g., baseline hemoglobin, baseline ferritin, baseline TSAT (serum tansferrin saturation) , baseline Hct, study center, EPO status, age group, gender, race and etc.) would be evaluated for inclusion in the final model. The model included treatment effect, covariates, and interaction between the treatment and each of the covariates. Covariates and their interactions considered statistically significant if p-value is <0.10. This step was done separately for each of the two primary efficacy parameters. However, the applicant was advised to select the covariates in the design stage of the study.

3.1.3 Detailed Review of Study 1VEN99012

Study 1VEN99012 was an open label, randomized, multi-center, active controlled, phase II/III study. Anemic patients with CRF, not receiving dialysis, who required iron supplementation and who met all of the inclusion criteria and had given informed consent were enrolled. The duration of each study for each patient was approximately 5 months. Screening of patients was performed and eligibility data were collected over 2 weeks, followed by 29 days of drug treatment and end-of-treatment evaluation on Day 43 (Treatment Phase). Each patient received either ferrous sulfate (325 mg orally three times a day on days 1 to 29) or Venofer (200 mg intravenous injection on days1, 8, 15, 22, and 29).

Efficacy assessments included hematologic parameters measured on days 15, 36, 43, and every 2 weeks thereafter and iron indices measured on days 36, 43, 57, 86,and 114. Safety assessments included recording of adverse events, physical examinations, vital signs, ECG and clinical laboratory test.

All patients (N=96) who received any amount of study medication had baseline hemoglobin values < 10.5 g/dL (or were granted exceptions for entry by Luitpold Pharamaceuticals , Inc.) and were included in the intent to treat population. Four patients in each of the treatment groups were received prohibited medications during the treatment phase and were excluded from the per protocol population. Efficacy results from the per protocol population were consistent with those seen for the intent to treat population; therefore, only results from the intent to treat population have been discussed herein.

An additional secondary variable was included in the efficacy analyses. The number of patients who achieved clinical success, defined as change in hemoglobin ≥0.8 g/dL and a change in serum ferritin >160 ng/mL from baseline up to Day 43, was tabulated.

Randomization:

Study medication was randomized in 1:1 ratio of intravenous iron sucrose: oral iron and was stratified by first time and previous users of epoetin. Sequential numbering was used across sites so that each patient number was unique. rovided the site a patient randomization number after confirmation of the inclusion/exclusion criteria stated in the protocol.

Sample Size Estimation:

The size of the samples was estimated based on 2 null hypotheses, each tested at 2.5% level of significance. A sample of size 39 patients was required to detect a difference in the change from baseline in hemoglobin level of 0.8g/dL at 805 power. A common standard deviation of 1.125g/dL was used in the computation. A sample of size of 39 patients was also adequate to detect a difference in the change from baseline in serum ferritin level of 160 ng/mL at 80% power. A common standard deviation of 220 ng/mL was assumed for the purpose of the estimation.

Efficacy Assessments:

The primary measures of efficacy were the mean changes from baseline to Day 43 in hemoglobin concentration and serum ferritin within each treatment group. Mean changes between Venofer and oral iron were also computed.

Secondary measures of efficacy were the change from baseline to Day 43 in hemotocrit (hct) and TSAT, the number of patients who attained hemgolobin > 11 g/dL during the study, the change from baseline to the end in epoetin and iron requirements, and change from baseline in QOL.

Safety:

Safety assessments included recording of adverse events, physical examinations, vital signs, ECG and clinical laboratory test.

Demographic and baseline Characteristics:

A summary of the demographic and baseline characteristics of the treatment groups is presented in Table A.1 in the Appendix. The applicant reported that there were no statistically significant differences between 2 treatment groups for any of the demographic baseline characteristics. Mean patient age 60 years old for the oral iron group and 62 years in Venofer group. The majority of the patients in both treatment groups were female (70% oral ironand 60% Venofer). The oral iron group was comprised primarily of Caucasians patients (44%) while the Venofer group was comprised primarily of "other" races (Hispanic 35%, Asian 2%, and Philipino 2%).

A summary of the baseline characteristics of the treatment groups is presented in Table A.2. It can be seen that the majority of the patients in both treatment groups were epoetin naïve (90% oral iron and 83% Venofer). Mean hemoglobin and SAT values at baseline were similar between the iron (10% g/dL and 15% respectively) and Venofer (10% g/dL and 17% , respectively) treatment groups. The proportion of patients with baseline TSAT < 20% was 81% in the oral group and 75% in the Venofer group. Mean ferritin at baseline was higher in the Venofer group (125.0 mg/mL) than in the oral group (103.0 ng/mL). The proportions of patients with baseline ferritin <100 ng/mL was 65% in the oral iron group and 44% in the Venofer group. Overall, 54.0% of the patients in the oral iron group and 33% of the patients in the Venofer group had baseline TSAT < 20% and ferritin <100 ng/mL.

The applicant reported that one oral iron patient had a poor history of iron tolerance (iron dextran). No other patients reported a prior history of iron tolerance.

Efficacy Analyses

The primary efficacy endpoints of the study were changes in hemoglobin and serum ferritin from baseline to Day 43 (end of treatment). The null hypotheses of interest was that there was no difference in hemoglobin and ferritin change from baseline to Day 43 between oral iron and intravenous iron sucrose. Analysis of covariance (ANCOVA) was used to evaluate the changes in hemogobin and ferritin level from baseline to Day 43. A paired sample t-test was used to evaluate from change from baseline within each treatment group at each visit.

The following table summarizes efficacy results for both hemoglobin and serum ferritin.

Table 2: Summary of Mean Changes From Baseline to Day 43 During the Treatment Phase (Extracted From Applicant's Volume 4, Table 6.4a and 6.4b)

Endpoint	Oral iron (N=48)			Venofer (N=48)			ANCOVA P-value LS [1] mean difference (Venofer – oral) (95% CI)
	Baseline	Change from baseline	p-value	Baseline	Change from Baseline	p-value	
Hemoglobin (Day 43)	9.7	0.7	<0.0001	9.9	1.0	<0.0001	0.14[2] 0.3 (-.01, 0.7)
serum ferritin	104	-5.1	0.365	110	288	<0.0001	<0.0001[3] 289.7 (246.39, 332.36)

1: LS (Least Squares)
2: Treatment, Baseline Ferritn, EPO status, and Race * Treatment in the model
3: Treatment, Baseline Ferritin, and Baseline Ferritin * Treatment in the model

Note that the applicant did not mention in the protocol what factor will be used in the ANCOVA model. The final model was identified by including treatment effect and all statistically significant covariates and interactions. The final model was used to estimate the overall effect and the nominal p-values for testing the difference beween 2 groups.

Hemoglobin:

It can be seen that from the above table that the difference between the treatment groups for the mean change from baseline to Day 43 in hemoglobin was not statistically significant.

Although statistically significant mean increases from baseline in hemoglobin was observed at day 43 in the Venofer group, this result cannot be taken as evidence for the efficacy of the Venofer.

Ferritin:

It can be seen from the above table that the difference between the treatments groups in mean change from baseline to days 43 in ferritin was statistically significant (p-value < 0.0001). Venofer group had statistically significant mean increases from baseline in ferritin values at Day 43. However, there was no statistically significant change from baseline in ferritin in the oral group at day 43. The mean change from baseline to Day 43 in ferritin was –5.1 ng/dL in the oral iron group. It appears that the significance difference between Venofer treated group and oral iron treated group is due negative change in ferritin values in the oral iron treated group.

Hemoglobin and ferritin as Joint Endpoint:

The applicant reported that changes in both hemoglobin and ferritin are determinants of response to iron-replacement therapy for iron-deficiency anemia. The applicant further reported that the most of the Venofer patients demonstrated percent increases from baseline to Day 43 in both hemoglobin and ferritin. The applicant claimed that small percent increases from baseline to Day 43 in hemoglobin were observed among most oral iron patients. However, very few demonstrated percent increases in ferritin. As hemoglobin and ferritin are interdependent and interrelated in the assessment of adequacy of iron replacement therapy in iron –deficiency anemia, the applicant conjectured that it may not be possible to precisely test for treatment effect on each parameter independently. Consequently, as a post-hoc analysis, the applicant conducted a multivariate analysis of variance (MANOVA) which tested the treatment difference of 2 dependent variables. The analysis used the MANOVA option in PROC GLM procedure, considering the percent changes from baseline to Day 43 in the hemoglobin and ferritin values a 2 dependent variables and treatment as the factor in the model. The results of this analysis indicated a statistically significant treatment effect (p-value <0.0001) for the test statistic of Wilks Lambda. The applicant concluded that the percent change from baseline to Day 43 for both hemoglobin and ferritin was statistically significantly different between the Venofer treated group and the oral iron treated group.

This reviewer computed Pearson correlation coefficient between change in hemoglobin from baseline and the change in serum ferritin from baseline. The Pearson correlation is almost zero (-0.0035). In addition, Pearson correlation coefficient between Hemoglon and serum ferritin at day 43 is 0.058. Thus the applicant's claim of hemoglobin and ferritin are interdependent and interrelated (in the assessment of adequacy of iron replacement therapy in iron –deficiency anemia) does not seem to be valid on the basis of the efficacy data.

This reviewer also computed Pearson correlation coefficient between percent change in hemoglobin and the percent change in serum ferritin. Although there is a significant (p-value=0.0429 for the hypothesis of no correlation) correlation between these two percentage changes, the Pearson correlation coefficient is 0.21. It is worth noting that percent change in hemoglobin and the percent change in serum ferritin are not endpoints defined in the protocol.

This reviewer conducted a separate analysis (ANCOVA with treatment and baseline hemoglobin /serum ferritin) based on the percent change from baseline
for both hemoglobin and ferritin. The percent change in hemoglobin from baseline to Day 43 was not significantly (p-value 0.2162) different between the Venofer treated group and oral iron treated group. However, the percent change in serum ferritin from baseline to Day 43 was significantly (p-value 0.0001) different between the Venofer treated group and oral iron treated group.

Although the applicant concluded that the percent change from baseline to Day 43 for both hemoglobin and ferritin was statistically significantly different between the Venofer treated group and the oral iron treated group, for approval purpose we need significance difference between the treated groups with respect to each primary endpoint.

3.1.4 Statistical Reviewer's Findings

As mentioned earlier that the applicant did not mention in the protocol what factor will be used in the ANCOVA model. The final model was identified by including treatment effect and all statistically significant covariates and interactions. The final model was used to estimate the overall effect and the nominal p-values for testing the difference beween 2 groups. This reviewer conducted analysis of covaraince for each parameter (hemoglobin/serum ferritin) using treatment and corresponding baseline (hemoglobin or serum ferritin) as covariate in the model. The results of these analyses are summarized in the following table.

Table 3: LS Mean Difference, Standard Error and ANCOVA P-value For Primary Endpoints

Endpoint	LS [1] mean difference (Venofer – oral)	Standard Error	ANCOVA P-value
Hemoglobin	0.30	0.21	0.16[2]
Serum ferritin	272.45	24.43	<0.0001[3]

1: LS (Least Squares)
2: Treatment and Baseline Hemoglobin in the model
3: Treatment and Baseline Ferritin in the model

It can be seen that from the above table that the difference between the treatment groups for the mean change from baseline to Day 43 in hemoglobin was not statistically significant. However, the difference between the treatments groups in mean change from baseline to days 43 in ferritin was statistically significant (p-value < 0.0001).

Therefore, the evidence taken from the single study reviewed does not indicate a support for the superiority of Venofer over oral iron in increasing hemoglobin from baseline to day 43 for CRF patients without hemodialysis.

Although the data reviewed indicates the superiority of Venofer in increasing serum ferritin for CRF patients not on hemodialysis when compared with oral iron, the control group did not have improvement at all in serum ferritin. The failure of the control group in improving serum ferritin contributed to the significant difference in the two treated groups. In fact, there was a negative change (-5.1) of serum ferritin from baseline with a standard deviation of 36.81 in the control group. Further there appears to be baseline imbalance in serum ferritin between oral iron treated group (mean serum ferritn 103 ng/mL) and Venofer treated group (mean serum ferritn 125 ng/mL). The negative change in serum ferritin at Day 43 from baseline plus lower mean ferritin level in the control group may have contributed toward the significant difference between the iron treated group and Venofer treated group. As a result, this single study cannot be taken as a basis of approval of 200 mg iron for CRF patients who are not on dialysis.

3.2 Evaluation of Safety

There were no statistical tests involved in assessing the significance of the safety parameters. In the following, we summarize the safety events for both groups.

The applicant reported that, during the treatment phase, the overall incidence of treatment emergent adverse events for the oral iron (90%) and Venofer (88%) were similar. Gastri-intestinal disorders were the most commonly experienced treatment-emergent adverse events in both treatment groups (48% oral iron and 35% Venofer). The most notable difference between the oral iron and Venofer groups during the treatment phase of the study was for the overall incidence of drug related gastro-intestinal (GI) disorders (35% oral iron and 13% Venofer). The difference in drug related GI disorders was primarily the result of increased incidence of constipation among patients in the oral iron group(15%) compared to the Venofer (0%). Additionally, drug related nausea (10% versus 4%, respectively), vomiting NOS (8% versus 0%, respectively) and diarrhea NOS (6% versus 0%, respectively)) were each experienced by a greater number of patients in the oral iron group compared to the Venofer group. The majority of treatment-emergent adverse events experienced during the treatment phase of the study were considered by the investigator to be mild or moderate in intensity.

A summary of treatment-emergent adverse events experienced by 3 or more patients in either treatment group during the treatment phase is presented in the following table.

Table 4: Treatment-Emergent Adverse Events Experienced by More Than 3 Patients in Either Treatment Group (Extracted From Applicant's Table 6.6.b, Volume 4)

At least One Treatment-Emergent adverse event	Oral iron (N=48)	**Venofer** (N=48)
Cardiac Disorders	8 (17%)	12 (25%)
Edema NOS	1 (2%)	4 (8%)
Hyperglycemia NOS	3 (2%)	47(15%)
Gastrointestinal Disorders	23 (48%)	17 (35%)
Nausea	8(17%)	12 (25%)

Diarrhea NOS Vomiting NOS Taste Disturbance Abdominal Pan NOS Constipation	5 (10%) 6(13%) 0 3 (6%)	5 (10%) 5 (10%) 4(8%) 2 (4%)
General Disorders and Administration Site conditions Injection site Burning Weakness	5 (10%) 0 3 (6%)	9 (19%) 0 0
Nervous system Disorders Dizziness (excluding Vertigo)	5 (10%) 1 (2%)	9 (19%) 4 (8%)
Respiratory, Thoracic, and Medistainal Disorders Nasal congestion	9 (19%) 3 (6%)	9 (19%) 1 (2%)
Skin and subcutaneous tissue disorders Pruritus NOS	12 (25%) 6 (12%)	6 (13%) 1 (2%)
Vascular Disorders Hypertension Aggravated	5 (10%) 1 (2%)	7 (15%) 4 (8%)

It can be seen that from the above table that Venofer treated patients had more cardiac disorders (25% versus 17%) and hyperglycemia NOS (15% versus 4%) than the oral iron treated group. Severe treatment-emergent adverse events were experienced by 1 patient (2%) in the oral iron group and 4 patients (8%) in the Venofer group. The severe treatment-emergent adverse events included one each of congestive cardiac failure, fluid overload, pulmonary edema NOS, diabetic ketoacidosis, pneumonia NOS, muscle cramps, hypovolemia, benign intracranial hypertension, and headache NOS. None of this these 9 severe events was considered by the Investigator to be study-drug related.

The applicant reported that during the treatment phase, at least one drug related treatment-emergent adverse event was experienced by 40% (19/48) of the patients in the oral iron group and 23% (11/48) of the patients in the Venofer group. A summary of the drug-related treatment-emergent adverse events are summarized in the following table.

Table 5: Drug-Related Treatment-Emergent Adverse Events Experienced by 3 or More Patients in Either Treatment group During the Treatment Phase (Extracted From Applicant's Table 6.6.c, Volume 4)

MedDRA SOC Preferred term	Oral iron (N=48)	Venofer (N=48)
At least One-Drug-Related Treatment –Emergent Adverse Event	19 (40%)	11 (23%)
Gastro-intestinal Disorders	17 (35%)	6 (13%)
Taste Disturbance	0	4 (8%)
Nausea	5 (10%)	2 (4%)
Constipation	7 (15%)	0
Vomiting NOS	4 (8%)	0
Diarrhea NOS	3 (6%)	0
General Disorders and Administration Site conditions	1 (2%)	4 (8%)
Injection site Burning	0	3 (6%)

The most commonly experienced drug related treatment emergent adverse events in the oral iron group were constipation (15%), nausea (10%), vomiting NOS (8%), and diarrhea NOS (6%). The most commonly drug-related treatment-emergent adverse events in the Venofer group were taste disturbance (8%), and injection site burning (6%).

Other Serious Events

During the treatment phase, 2 (4%) oral iron patients and 7 (15%) Venofer patients experienced at least one serious adverse event. None of these serious adverse events reported during the treatment phase was considered by the investigator to be related to study medication or epoetin administration.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

This reviewer conducted treatment by sub-group (e.g., gender, age-group, and race) interaction tests using the ANCOVA (baseline hemoglobin as a covariate) model with treatment-group, sub-group and sub-group x treatment -group as fixed effects. Note that the trial was not sized for testing subgroup by treatment interaction. Subgroup analyses are summarized as follows.

Gender:

Hemoglobin:

This reviewer conducted treatment by the gender interaction test using the ANCOVA (baseline hemoglobin as a covariate) model with treatment-group, gender and gender x treatment -group as fixed effects. The test failed to detect that the interaction (p-value 0.2412) between gender and the treatment-group. It can be seen that females who received Venofer had greater mean increases than the oral group in the mean change from baseline at Day 43 in hemoglobin. However, male who received oral iron had greater mean increase in hemoglobin than the patients who received Venofer. Table A.4 summarizes changes in hemoglobin from baseline to Day 43.

Serum ferritin:

This reviewer conducted treatment by the gender interaction test using the ANCOVA (baseline hemoglobin as a covariate) model with treatment-group, gender and gender x treatment -group as fixed effects. The test failed to detect that the interaction (p-value 0.9400) between gender and the treatment-group. The subgroup analysis of changes in serum ferritin from baseline to Day 43 by gender showed that, in either sex, subjects receiving treatment with the Venofer had had greater mean increases than the oral group in the mean change from baseline at Day 43 in serum ferritin Table A.4 summarizes changes in serum ferritin from baseline to Day 43.

Age-group:

Hemoglobin:

This reviewer conducted treatment by the age-group interaction test using the ANCOVA (baseline hemoglobin as a covariate) model with treatment-group, age-group and age-group x treatment-group as fixed effects. The test failed to detect that the interaction (p-value 0.6019) between gender and the treatment-group. Table A.3 (in Appendix) summarizes the event rates in the two treatment groups by gender for the primary efficacy patient population. It can be seen that regardless of age (<65 or ≥ 65), patients who received Venofer had greater mean increases than the oral iron group in the mean change from baseline to Day 43 in feriitin.

Serum ferritin:

This reviewer conducted treatment by the gender interaction test using the ANCOVA (baseline hemoglobin as a covariate) model with treatment-group, age-group and age-group x treatment -group as fixed effects. The test failed to detect that the interaction (p-value 0.7442) between gender and the treatment-group. Table A.4 summarizes the event rates in the two treatment groups by gender for the primary efficacy patient population. It can be seen that regardless of age (<65 or ≥ 65), patients who received Venofer had greater mean increases than the oral iron group in the mean change from baseline to Day 43 in feriitin.

Race:

Hemoglobin:

This reviewer conducted treatment by the race interaction test using the ANCOVA model (baseline hemoglobin as a covariate) treatment group, race and race x treatment -group as fixed effects. The test failed to detect that the interaction (p-value 0.3183) between race and the treatment-group. Table A.5 summarizes changes in hemoglobin from baseline to Day 43. It can be seen that blacks and others races who received Venofer had greater mean increases than the oral iron group in the mean change in hemoglobin from baseline to Day 43. However, Caucasians who received oral iron had greater mean increase s in hemoglobin than the Caucasians who received Venofer.

Serum ferritin:

This reviewer conducted treatment by the race interaction test using the ACNOVA model (baseline hemoglobin as a covariate) treatment group, race and race x treatment -group as fixed effects. The test failed to detect that the interaction (p-value 0.1539) between race and the treatment-group. Table A.5 summarizes changes in serum ferritin from baseline to Day 43. Regardless of race, patients who receive Venofer had greater mean increases than the oral iron group in the mean change from baseline in the men change from baseline to Day 43 in serum ferritin.

4.2 Other Special/Subgroup Populations

Center:

Hemoglobin:

This reviewer conducted treatment by the site interaction test using the ANCOVA model treatment group, site (pooled) and site x treatment-group as fixed effects. The test failed to detect that the interaction (p-value 0.3573) between site and the treatment-group. Table A.6 summarizes changes in hemoglobin from baseline to Day 43. It can be seen that only in pooled center f, oral iron treated group had numerically higher mean increases than the Venofer treated group in the mean change from baseline to Day 43 in hemoglobin.

Serum ferritin:

This reviewer conducted treatment by the site interaction test using the ANCOVA model treatment group, site and site x treatment-group as fixed effects. The test failed to detect that the interaction (p-value 0.7492) between site and the treatment-group. Table A.7 summarizes changes in serum ferritin from baseline to Day 43. egardless of center, patients who received Venofer had greater mean increases than the oral iron group in the mean change from baseline to Day 43 in ferritin.

Epoetin Status

Note that about 90% percent of the patients in the iron treated group were new epoetin user where as 83% percent of the Venofer treated group were new epoetin users. The following table summarizes the mean changes in hemoglobin from baseline to day 43 with respect to epoetin status at the beginning of the trial.

Table 6: Mean Difference, 95% Confidence Interval (CI) and ANOVA P-value For Change in Hemoglobin

Epoetin status	Oral Iron (95% CI)	Venofer (95% CI)	LS mean difference (Venofer – Oral) (95% CI)	ANOVA P-value
New epoetin users	0.81 (0.50, 1.12)	1.10 (0.76, 1.44)	0.29 (-0.17, 0.75)	0.21
Previous epoetin users	0.06 (-1.02, 1.15)	0.69 (-0.73, 1.98)	0.62 (-0.73, 1.98)	0.33

The data reviewed indicated that the new epoetin users in both Venofer treated group and control group had significant improvement in hemoglobin where as previous epoetin user patients in both Venofer and oral iron treated groups did not have significant improvement in hemoglobin.

Table 7: Mean Difference, 95% Confidence Interval (CI) and ANOVA P-value For Serum Ferritin

Epoetin status	Oral Iron (95% CI)	Venofer (95% CI)	LS mean difference (Venofer – Oral) (95% CI)	ANOVA P-value
New epoetin users	-6.14 (-43.1, 30.78)	296.5 (255.3, 337.8)	302.7 (247.3, 358.1)	<0.0001
Previous epoetin users	5.53 (-116, 127.2)	249.2 (157.2, 341.2)	243.7 (91.14, 396.2)	0.006

It can be seen from the above table that oral iron was not effective in improving serum ferritin for both new epoetin user patients and previous epoetin user patients. It appears that the oral iron is not effective all in improving serum ferritin for CRF patients not on dialysis.

This reviewer found that subgroup analyses of changes of serum ferritin from baseline to Day 43 by gender, race and age-group showed that Venofer treated group had more increases in serium ferritin from baseline to day 43 than the oral iron treated group.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

As mentioned earlier, Venofer was originally approved for ESRD (end stage renal disease) patients on the basis of 100 mg of iron sucrose injection given over 5 minutes per dialysis session and up to a total dose 1,000 for each treatment cycle. The current submission of Venofer for 200 mg dose was proposed for CRF patients who were not on dialysis. The efficacy data from this submission does not adequately show that Venofer 200 mg is effective in increasing hemoglobin level of CRF patients who are not on dialysis. Although the data reviewed indicates the superiority of Venofer in increasing serum ferritin for CRF patients not on hemodialysis when compared with oral iron, the control group did not have improvement at all in serum ferritin which contributed to the significant difference in the two treated groups.

As a post-hoc analysis, the applicant conducted a MANOVA which tested the treatment difference of 2 variables. The analysis used the MANOVA option in the PROC GLM procedure, considering the changes from baseline to Day 43 in hemogolobin and ferritin values as 2 dependent variables and treatment as a factor in the model. The results of this analysis indicated a statistically significant treatment effect (p-value <0.0001) for the test statistics Wilk's Lambda. However, the percentage change in hemoglobin was not different between the Venofer treated group and oral iron treated group. Note that percentage change was not defined as an endpoint in the protocol, and the MANOVA procedure was conducted after the fact there was no significant difference between the two groups with respect to the first primary end point (change in hemoglobin). Both primary endpoints needed to show significance in order to show the efficacy of the drug.

The applicant submitted three studies from the original NDA and three studies from the literature as a supporting study. Three studies A, B and C from the original NDA were for the ESRD patients undergoing kidney dialysis. The patient population and dosing regimens in these three studies are different from the current submission. Thus, it is not possible to use the efficacy and safety data of approved dose (100 mg) for ESRD patients on dialysis to support the efficacy and safety of proposed Venofer dose for CRF patients without dialysis. Note that the patient populations are different as well as the dosing regimens.

In addition, the three studies (cited from the literature) do not adequately serve as supporting studies for the current submission because the studies varied from the current submission in that they were conducted earlier in the trial process, used different designs, different phases and

dosage strengths, and /or defined the primary efficacy variable differently. Only one (Stoves et al. 2001) of these 3 studies cited from the literature is an active controlled (oral iron) study. However, Venofer dose level (300 mg) and oral iron dose level (200 mg) were different from the pivotal study.

5.2 Conclusions and Recommendations

The evidence taken from the single study reviewed does not indicate a support for the superiority of Venofer over oral iron in increasing hemoglobin from baseline to day 43. efficacy and safety of Venofer for CRF patients without hemodialysis.

Although the data reviewed indicates the superiority of Venofer in increasing serum ferritin for CRF patients not on hemodialysis when compared with oral iron, the control group did not have improvement at all in serum ferritin. The failure of the control group in improving serum ferritin contributed to the significant difference between the two treated groups. In fact, there was a negative change (-5.1) of serum ferritin from baseline with a standard deviation of 36.81 in the control group. Further there appears to be baseline imbalance in serum ferritin between oral iron treated group (mean serum ferritn 103 ng/mL) and Venofer treated group (mean serum ferritn 125 ng/mL). The negative change in serum ferritin at Day 43 from baseline plus lower mean baseline ferritin level in the control group may have contributed toward the significant difference between the iron treated group and Venofer treated group. As a result, this single study cannot be taken as a basis of approval of Venofer 200 mg for CRF patients who are not on dialysis.

The safety data showed that during the treatment phase, the overall incidence of treatment emergent adverse events for the oral iron (90%) and Venofer (88%) were comparable. Gastro-intestinal disorders were the most commonly experienced treatment-emergent adverse events in both treatment groups (48% oral iron and 35% Venofer). In particular, Venofer treated patients had more cardiac disorders (25% versus 17%) and hyperglycemia NOS (8% versus 4) than the oral iron treated group. The safety data also showed that during the treatment phase, overall (at least one) drug related treatment-emergent adverse event experienced by the Venofer treated group (23%) and the oral iron treated group (40%) were comparable. Gastro-intestinal disorders were the most commonly experienced drug related treatment-emergent adverse events in both treatment groups (35% oral iron and 13% Venofer).

In order to receive an approval for Venofer 200 mg, the applicant is suggested to conduct another trial with CRF patients without dialysis. The applicant may consider placebo controlled trial or adding a placebo arm along with an oral iron treated arm in the new trial.

APPENDIX

The appendix contains demographic/baseline characteristics and subgroup analyses tables

Table A.1: Patient's Demographic Characteristics (extracted from applicant's Table 6.2a, Volume 4)

Demographic Characteristics	Oral Iron (N=48)	Venofer (N=48)
Age (years)		
≤65	29 (60%)	22(46%)
>65	19(40%)	26(54%)
Sex		
Male	14 (29%)	19(40%)
Female	34 (71%)	18(60 %)
Race :		
Black	14 (29%)	11 (23%)
Caucasian	21 (44%)	18 (38%)
Others	13 (27%)	19 (40%)
Weight (kg)	(N=46)	(N=48)
Mean (SD)	84.0 (19.2)	84.2 (24.3)

Table A.2: Patient's Baseline Characteristics (extracted from applicant's Table 6b, Volume 4)

Baseline Characteristics	Oral Iron (N=48)	Venofer (N=48)
Epoetin Status		