# CLINICAL REVIEW

| | |
|---|---|
| Application Type | NDA |
| Application Number(s) | 21135/S024 |
| Priority or Standard | Standard |
| Submit Date(s) | September 6, 2011, April 27, 2012 |
| Received Date(s) | September 7, 2011, April 30, 2012 |
| PDUFA Goal Date | October 7, 2012 |
| Division / Office | DHP/OHOP |
| Reviewer Name(s) | Min Lu, M.D., M.P.H. |
| Review Completion Date | August 16, 2012 |
| Established Name | Iron Sucrose Injection |
| (Proposed) Trade Name | Venofer |
| Therapeutic Class | Iron replacement product |
| Applicant | Luitpold Pharmaceuticals, Inc. |
| Formulation(s) | 100 mg of elemental iron/5 mL vials |
| Dosing Regimen | 0.5 mg/kg, (b) (4) Maximum single dose of 100 mg |
| Indication(s) | Treatment of iron deficiency anemia |
| Intended Population(s) | Pediatric population with chronic kidney disease |

**Table of Contents**

**Table of Tables**

## Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| AST | Aspartate Aminotransferase |
| BUN | Blood Urea Nitrogen |
| CKD | Chronic Kidney Disease |
| dL | Deciliter |
| ECG | Electrocardiogram |
| EPO | Erythropoietin |
| g | Gram |
| GFR | Glomerular Filtration rate |
| Hb (Hgb) | Hemoglobin |
| HDD-CKD | Hemodialysis Dependent Chronic Kidney Disease |
| IND | Investigational Drug Application |
| ITT | Intent-to-Treat |
| IV | Intravenous |
| kg | Kilogram |
| MCH | Mean Corpuscular Hemoglobin |
| MCHC | Mean Corpuscular Hemoglobin Concentration |
| MCV | Mean Corpuscular Volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | Modified Intent-to-Treat |
| mg | Milligram |
| mL | Milliliter |
| rnrnHg | Millimeters Mercury |
| NDA | New Drug Application |
| NDD-CKD | Non-dialysis dependent chronic kidney disease |
| ng | Nanogram |
| PD-CKD | Peritoneal dialysis dependent CKD |
| PK | Phamacokinetics |
| PMC | Postmarket Commitment |
| PREA | Pediatric Research Equity Act |
| RBC | Red Blood Cell |
| SAE | Serious Adverse Event |
| SD | Standard Deviation |
| SOC | System Organ Class |
| TSAT | Transferrin Saturation |
| U.S. | United States |
| WBC | White Blood Cell |

# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

From a clinical perspective, this reviewer recommends Venofer be approved for the proposed indication for the treatment of iron deficiency anemia in pediatric patients with chronic kidney disease (CKD).

With this supplement, the applicant has fulfilled the pediatric study requirement under PREA for following deferred pediatric studies and the PMC#3 issued when Venofer was approved initially.

- Deferred pediatric study under PREA for the treatment of for hemodialysis dependent-chronic kidney disease (HDD-CKD) patients receiving an erythropoietin in pediatric patients (issued November 30, 2005).
- Deferred pediatric study under PREA for the treatment of iron deficiency anemia in non-dialysis-dependent chronic kidney disease (NDD-CKD) pediatric patients ages greater than or equal to two years to less than 12 years receiving or not receiving erythropoietin (issued June 17, 2005).
- An adequate and well-controlled clinical trial of safety and efficacy of Venofer in the treatment of iron deficiency in children (aged 2 to 12 years) who are on hemodialysis and receive epoetin. (Use of an active control, such as an oral iron, or dose ranging comparison should be considered in designing this study). (PMC#3, issued November 6, 2000)

## 1.2 Risk Benefit Assessment

The risk benefit assessment is favorable for Venofer at dose of 0.5 mg/kg as iron maintenance treatment in pediatric patients with CKD. Patients in the Venofer 0.5 mg/kg group experienced less treatment-emergent serious adverse events and less drug-related adverse reactions than those in the Venofer 1.0 mg/kg and 2.0 mg/kg groups. The proportion of patients with stable erythropoietin dosing who had maintained hemoglobin between 10.5 g/dL and 14.0 g/dL during the 12-week treatment period was highest in the Venofer 0.5 mg/kg group among the three Venofer dose groups.

## 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

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

## 1.4 Recommendations for Postmarket Requirements and Commitments

This submission is in response to PMRs and PMC. Since it is likely that pediatric patients will receive repeated courses of Venofer for iron maintenance treatment, consideration should be given to seeking collection of safety data with chronic use of Venofer in these patients.

# 2 Introduction and Regulatory Background

## 2.1 Product Information

Drug established name: Iron sucrose injection
Proposed trade name: Venofer
Chemical class: Intravenous iron products
Pharmaceutical class: Anti-anemia products
Proposed indication: Treatment of iron deficiency anemia in (b) (4) patients (b) (4) with chronic kidney disease.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

Current available treatment for iron deficiency anemia includes oral iron products and intravenous iron products. The approved intravenous iron products in the U.S. include Iron dextran (INFeD and Dexferrum), Ferrlecit, Venofer, and Feraheme. The approved indications, dose regimens and main safety concerns for these intravenous iron products are shown in the table below. Iron dextran has total dose recommendation on labeling for pediatric patients. Ferrlecit is approved for pediatric patients age 6 years and older with chronic kidney disease (CKD) receiving hemodialysis.

**Table 1. Currently Approved Intravenous Iron Products in US**

| Chemical name | Iron Dextran (INFeD, Dexferrum) | Ferrlecit (Sodium Ferric gluconate complex) | Venofer (Iron Sucrose) | Feraheme (ferumoxytol) |
|---|---|---|---|---|
| Year of first U.S. approval | 1974 | 1999 (marketed in Europe since 1950's) | 2000 (marketed in Europe since 1950's) | 2009 |
| Indication | Treatment of patients with documented iron deficiency anemia in whom oral iron administration is unsatisfactory or impossible | Treatment of iron deficiency anemia in adult patients and in pediatric patients age 6 years and older with chronic kidney disease receiving hemodialysis who are receiving supplemental epoetin therapy | Treatment of iron deficiency anemia in adult patients with chronic kidney disease | Treatment of iron deficiency anemia in adult patients with chronic kidney disease |
| Safety | Box warning for anaphylactic-type reactions | Warning for hypersensitivity reactions | Warning for hypersensitivity reactions | Warning for hypersensitivity reactions |
| Population | Adults and Pediatrics | Adults and Pediatrics | Adults | Adults |
| Dose regimen | 100 mg (2 mL) may be given on a daily basis until the calculated total amount required has | Adults:<br>Total cumulative dose: 1,000 mg<br><br>125 mg for 8 doses at | Total cumulative dose: 1,000 mg<br><br>Hemodialysis:<br>100 mg for 10 doses | Total cumulative dose: 1020 mg<br>510 mg intravenous injection followed by a second 510 mg |

| | | | | |
|---|---|---|---|---|
| | been reached. It is given undiluted at a slow gradual rate not to exceed 50 mg per minute.<br><br>Adults and Children over 15 kg (33 lbs): Total amount (mL) = 0.0442 (Desired Hb-Observed Hb) × LBW (kg) + (0.26 × LBW)<br><br>Children 5-15 kg (11-33 lbs): Total amount (mL) = 0.0442 (Desired Hb-Observed Hb) × W (kg) + (0.26 ×W)<br><br>Each mL contains 50 mg of elemental iron.<br><br>A test dose (0.5 mL) is required before the dosing. | sequential dialysis session, by slow injection at a rate of up to 12.5 mg/min or infusion over 1 hour diluted in 100 mL of 0.9% sodium chloride.<br><br>Pediatrics: 1.5 mg/kg diluted in 25 mL 0.9% sodium chloride and administered by intravenous infusion over 1 hour per dialysis session. The maximum dosage should not exceed 125 mg per dose | at consecutive dialysis session, as slow IV injection or as an infusion diluted in a 100mL of 0.9% NaCl over at least 15 minutes<br><br>Non-Dialysis Dependent-Chronic Kidney Disease: 200 mg for 5 doses within the 14 day period as slow IV injection. Limited experience with 500 mg for 2 doses on day 1 and day 14, diluted in a maximum of 250 mL of 0.9% NaCl, over a period of 3.5 to 4 hours.<br><br>Peritoneal Dialysis: 300 mg for 2 doses 14 days apart, as infusion diluted in a maximum of 250mL of 0.9% NaCl. over 1.5 hours, followed by 400 mg infusion over 2.5 hours 14 days later. | intravenous injection 3 to 8 days later. Administer Feraheme as an undiluted intravenous injection delivered at a rate of up to 1 mL/sec (30 mg/sec). |

## 2.3 Availability of Proposed Active Ingredient in the United States

Iron sucrose is available in the U.S. There are five intravenous iron products including Venofer available in the U.S. as described above.

## 2.4 Important Safety Issues With Consideration to Related Drugs

Intravenous iron products have been associated with anaphylactic-type reactions. Iron dextran products (INFeD and Dexferrum) have a boxed warning for anaphylactic-type reactions. Ferrlecit, Venofer and Feraheme have bolded warnings for hypersensitivity reactions.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Two PMCs for pediatric studies were issued in November 6, 2000 at the Venofer initial approval including PMC #2 and #3 as follows.

PMC#2: A single-dose, pharmacokinetics study of Venofer following intravenous administration to adolescent hemodialysis patients on epoetin

PMC#3: An adequate and well-controlled clinical trial of safety and efficacy of Venofer in the treatment of iron deficiency in children (aged 2 to 12 years) who are on hemodialysis and receive epoetin (use of an active control, such as oral iron, or dose ranging comparison should be considered in designing this study)

On November 20, 2001, the applicant submitted the protocol for PMC#2 PK study. In the study protocol, the proposed study patients would not be iron deficient according to the inclusion criteria (serum ferritin <800 ng/ml and transferrin saturation <50%). Considering that the PK profile may be different between adolescents with and without iron deficiency, the Division recommended that patients in the proposed study should be adolescents with iron deficiency defined by hemoglobin ≤11 g/dL with serum transferrin saturation < 20% or serum ferritin < 100 ng/mL (dated April 26, 2002).

On May 2, 2002, in response to the Division's recommendation, the applicant submitted additional information asserting there was an insufficient number of pediatric patients on hemodialysis available with the recommended eligible criteria due to aggressive treatment with erythropoietin therapy and IV iron in US dialysis centers. The sponsor also provided a published paper titled "Longitudinal Analysis of Pediatric (> 12 - < 18 years old) In-Center Hemodialysis Patients", a supplemental report for ESRD Clinical Performance Measures Project by Centers for Medicare and Medicaid Services (February 2002). The report included 435 patients aged 12 to <18 years (206 in 12-15 years age range and 229 in 16 to <18 years age range) collected in the 18 ESRD Network in U.S. in 2000-2001. It showed that 55%-75% of patients had a mean hemoglobin ≥11 gm/dL, 69%-80% of patients had TSAT ≥20%, and 70-82% of patients had serum ferritin ≥100 ng/mL. The sponsor also attached a letter from (b) (4) , which indicated that <8% of adolescent patients in Northwestern University's Renal Network had hemoglobin values < 11 gm/dL, no patients had TSAT <20% and only 17% had serum ferritin levels <100 ng/mL.

(b) (4)

The Division reviewed the submitted information and considered that maintenance iron therapy may also be important in pediatric patients on hemodialysis if only few patients developed iron deficiency with standard of care management in current clinic practice. Studies to identify appropriate maintenance dosing of Venofer to prevent iron deficiency in the pediatric population undergoing chronic hemodialysis may be useful to clinic practice (Dr. Min Lu, 7/1/02). The Division issued a letter on 6/2/2003 regarding PMC #3 and stated that the sponsor should conduct a pediatric study as specified in the PMC and allowed that the study may be designed to

identify an appropriate maintenance dose of Venofer in the pediatric population undergoing chronic hemodialysis.

The PK study report in patients undergoing hemodialysis in response to PMC#2 was submitted on December 16, 2003. Both clinical pharmacology and clinical reviewed the study report. The PMC#2 was considered to be fulfilled.

On December 23, 2003, the applicant submitted a study protocol for PMC#3 (Protocol No. 1VEN03017) which was reviewed by the Division (Dr Min Lu, dated 2/17/04). The proposed study was a randomized, open-label, dose-ranging trial (0.5mg/kg, 1 mg/kg and 2mg/kg) in 45 patients aged 2 to 21 years who have CKD, are undergoing peritoneal dialysis or hemodialysis, receiving erythropoietin therapy and having hemoglobin between 11.0 and 14.0 g/dL. The primary objective of this trial is to assess the safety of Venofer in children who are undergoing peritoneal dialysis or hemodialysis and receiving erythropoietin therapy in an effort to maintain hemoglobin over a 3 month period. The secondary objective was to determine dosing required to maintain the hemoglobin within 10% of the baseline value. The sample size was based on a Chi-square test of equal proportions, at 90% power and an alpha level at 0.5, with assumption of a 15% maintenance rate in the 0.5 mg/kg Venofer group, a 40% maintenance rate in the 1.0 mg/kg group, and 80% maintenance rate in the 2.0 mg/kg group. "Maintenance" was defined as a hemoglobin level within ±10% of the patient's baseline Hgb level. The applicant did not specify how many patients in the study would be in age 2-12 year group. The Division recommended the study include an adequate number of patients at age between 2 to 12 years in the study to allow the evaluation of safety and efficacy in this population (letter dated 3/5/04).

The Pediatric Research Equity Act (PREA) was enacted on December 3, 2003. Under PREA, the applicant was requested to submit a pediatric plan (letter dated March 1, 2005). The applicant requested a deferral for pediatric study on June 28, 2005 and requested to use the proposed study 1VEN03017 for PMC#3 to meet the PREA requirement. The Division agreed and issued a deferred pediatric study under PMC on November 30, 2005:

1. Deferred pediatric study under PREA for the treatment of iron deficiency anemia for hemodialysis dependent CKD patients receiving an erythropoietin in pediatric patients.

On June 17, 2005, a supplemental NDA (S-008) for Venofer was approved for non-dialysis dependent CKD population and two additional deferred pediatric studies under PMC were issued under PREA per the applicant's request:

1. Deferred pediatric study under PREA for a pharmacokinetic (PK) 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.

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

The pediatric study requirement for age birth to <2 years was waived due to insufficient number of patients available for study.

On June 17, 2005, the applicant requested a modification for #2 and proposed to include patients with non-dialysis dependent CKD in the protocol 1VEN03017 to study the maintenance dose of Venofer.

On September 21, 2005, the sponsor submitted an amended protocol 1VEN03017 to include patients with NDD-CKD and expanded up to 60 subjects and the efficacy endpoint including clinical success defined as hemoglobin between 10.5 g/dl - 14.0g/dL, TSAT between 20%-50% and stable erythropoietin dosing (+/- 25% of baseline dose) or a decrease more than 25% in erythropoietin dosing. The Division reviewed the protocol (Dr. Andrew Dmytrijuk, dated 11/30/05) and recommended to increase the number of patients to 120 patients stratified by HD-CKD or non-HD-CKD (20 patients in each of 3 dosing groups for HD-CKD and non-HD-CHD) and additional efficacy analysis (letter dated 12/08/05).

The PK study of Venofer in pediatric patients with non-dialysis CKD was submitted on April 16, 2010 and labeling update is requested by FDA clinical pharmacology review (Dr. Bahru A Habtemariam, Pharm.D., dated 4/8/2011). Some information from the PK study was included in the label with the approval of PLR labeling conversion (S-20) on 6/22/11.

This supplemental NDA submission included a study report of 1VEN03017 for a pediatric indication. It also intended to fulfill PMC#3 issued in 2000 (dialysis CKD) and to meet requirements under PREA for a deferred pediatric study issued on November 30, 2005 (dialysis CKD) and a deferred pediatric study #2 issued on June 17, 2005 (non-dialysis CKD).

The applicant also resubmitted PK study in this supplement for labeling update purpose.

### 2.6 Other Relevant Background Information

Venofer was initially approved in 2000 in U.S. and had been marketed over 50 years in Europe prior to US approval.

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

This NDA supplement is submitted in paper. No clinical site inspections were planned for this supplement.

### 3.2 Compliance with Good Clinical Practices

The clinical trial was conducted in accordance with accepted ethical standards, in compliance with Good Clinical Practice.

### 3.3 Financial Disclosures

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

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

CMC review is pending.

### 4.2 Clinical Microbiology

The review is pending.

### 4.3 Preclinical Pharmacology/Toxicology

No new information was provided.

### 4.4 Clinical Pharmacology

#### 4.4.1 Mechanism of Action

Following intravenous administration, Venofer is dissociated into iron and sucrose and the iron is transported as a complex with transferrin to target cells including erythroid precursor cells. The iron in the precursor cells is incorporated into hemoglobin as the cells mature into red blood cells.

#### 4.4.2 Pharmacodynamics

No new data were submitted.

#### 4.4.3 Pharmacokinetics

A single dose PK study (1VEN05033) in pediatric patients 12 to 16 years of age with NDD-CKD was conducted in response to PMC. Patients were treated with a single intravenous Venofer dose of 7 mg/kg with the maximum dose of 200 mg. Eleven patients were enrolled and 9 patients had pharmacokinetic data. The submitted PK results showed that female children have lower Cmax

(36%) and longer half life (46%) than males. When comparing pediatric PK data with adult PK data, children appear to have higher dose adjusted Cmax and AUC than adults. Compared to the referenced adult PK data in the original NDA, the Cmax and AUC of total serum iron were 1.42- and 1.67-fold higher. However, these findings were limited to a relatively small sample size and it is unclear if comparable analytical methods was used between adults and children (see FDA Clinical Pharmacology Review, Dr. Bahru A Habtemariam, Pharm.D., dated 4/8/2011). The Clinical Pharmacology review recommended to include the following in the product label:

> **Pharmacokinetics in Pediatric Patients**
> In a single-dose PK study of Venofer in NDD-CDK patients ages 12 to 16 (N=11), patients received intravenous bolus doses of 7 mg/kg (maximum 200 mg) Venofer administered over 5 minutes. Total serum iron increased rapidly following the 5-minute intravenous dose. Following single dose Venofer, the half-life of total serum was 8.04 hours. The mean Cmax and AUC values were 8545 µg/dL and 31305 hr•µg/dL, respectively, which were 1.42- and 1.67-fold higher than dose adjusted adult Cmax and AUC values.

Language similar to the recommended was incorporated in the label with the approval of the PLR labeling for Venofer on 6/22/11.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

**Table 2. Table of Clinical Trial**

| Study | Type of trial | Number of patients enrolled | Dosing groups | Location |
|---|---|---|---|---|
| 1VEN03017 | Multi-center, Randomized, open-label, dose-range study | 145 patients with CKD<br>Age groups:<br>2-5 years: 10 patients<br>6-11 years: 31 patients<br>12-17 years: 81 patients<br>18-20 years: 23 patients | Venofer:<br>0.5 mg/kg: 49 patients<br>1.0 mg/kg: 47 patients<br>2.0 mg/kg: 49 patients | 28 centers<br>United States and Russia |

### 5.2 Review Strategy

One randomized dose-response trial was submitted and reviewed for efficacy and safety for the proposed pediatric indication.

### 5.3 Discussion of Individual Studies/Clinical Trials

Study 1VEN03017 was a randomized, open-label, three-dose level (0.5 mg/kg, 1.0 mg/g, or 2.0 mg/kg), parallel-group study in 145 patients 2 to 20 years of age with CKD on stable EPO therapy. The primary objective of this study was to compare the safety of three Venofer iron

maintenance regimens over a 12-week period in EPO treated pediatric patients with CKD. Patients who had hemoglobin level between 11.0 and 14.0 g/dL without iron depletion were randomized to one of three Venofer maintenance dosing groups. The efficacy endpoints were considered as the secondary endpoints of the study. The main efficacy endpoint was "Clinical success" defined as to maintain hemoglobin (10.5-14 g/dL) and TSAT (20-50%) with stable EPO dosing.

The regulatory history of the pediatric plan and this study has been discussed in detail in Section 2.5. Due to an insufficient number of pediatric patients with CKD and iron deficiency anemia available, this study was designed to collect the safety information for three Venofer doses as iron maintenance treatment in this pediatric population to better reflect clinical practice.

## 6 Review of Efficacy

***Efficacy Summary***

Study 1VEN03017 was a randomized, open-label, dose-ranging study for maintenance treatment in pediatric patients with CKD on stable erythropoietin therapy. The primary objective of this study was to compare the safety of three Venofer iron maintenance regimens (0.5 mg/kg, 1.0 mg/kg or 2.0 mg/kg) over a 12-week period in EPO treated pediatric patients with CKD. The efficacy endpoints were considered as the secondary endpoints of the study.

A total of 145 patients were enrolled in the study with 10 patients age 2-5 years, 31 patients age 6-11 years and 81 patients age 12-17 years. The mean age was 13 years (range 2 to 20 years). Over 70% of subjects were 12 years or older in all 3 dose groups. There were 84 males and 61 females. About 60% of subjects underwent hemodialysis (91 patients) and 25% underwent peritoneal dialysis (36 patients) in all three dose groups. At baseline, the mean hemoglobin was 12 g/dL, the mean TSAT was 33% and the mean ferritin was 300 ng/mL. Patients with hemodialysis dependent CKD (HDD-CKD) received a Venofer dose once every other week for 6 doses. Patients with peritoneal dialysis dependent CKD (PDD-CKD) and non-dialysis dependent CKD (NDD-CKD) received a Venofer dose once every 4 weeks for 3 doses.

Of 145 randomized patients, 131 subjects who received at least 1 dose of study drug, had a stable EPO dose for at least 8 weeks before randomization, and had at least 1 post-baseline hemoglobin and ferritin assessment were included in the modified ITT (mITT) Population.

Among 131 evaluable subjects, the proportions of patients who achieved clinical success (defined as hemoglobin 10.5-14 g/dl, TSAT 20-50% and stable EPO dosing) were 26.1%, 22.2%, and 30% in the Venofer 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg, respectively. The proportions of patients who maintained hemoglobin between 10.5 g/dL and 14.0 g/dL during the 12-week treatment period with a stable erythropoietin dosing were 58.7%, 46.7%, and 45.0% in the Venofer 0.5mg/kg, 1.0mg/kg, and 2.0 mg/kg, respectively. The proportions of patients who maintained TSAT between 20% and 50% were 32.6%, 40%, and 50% in the Venofer 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg, respectively. A dose-response relationship was not demonstrated.

## 6.1 Indication

The sponsor proposes [redacted] (b) (4) to the currently approved indication for the treatment of iron deficiency anemia in [redacted] (b) (4) patients with chronic kidney disease (CKD), such that the indication would read, "Venofer is indicated for the treatment of iron deficiency anemia in [redacted] (b) (4) patients [redacted] (b) (4) with chronic kidney disease".

### 6.1.1 Methods

The sponsor conducted one clinical trial (1VEN03017) in pediatric patients with CKD to evaluate the efficacy of Venofer for the proposed inclusion of pediatric patients [redacted] (b) (4).

The following is a summary of Study 1VEN03017 protocol.

*Title of Study:*
Comparison of the Safety and Efficacy of Three Venofer Iron Maintenance Regimens in Pediatric Chronic Kidney Disease Patients

*Study Objective:*
The primary objective of this study was to compare the safety of three Venofer iron maintenance regimens over a 12-week period in EPO treated pediatric CKD subjects.

*Study Design:*
The study was a randomized, open-label, three-dose level (0.5 mg/kg, 1.0 mg/g, or 2.0 mg/kg), parallel-group study in pediatric patients with CKD on stable EPO therapy. At the time of randomization, subjects were stratified according to dialysis status [hemodialysis-dependent (HDD) or non-HDD including either peritoneal dialysis dependent (PDD) or non-dialysis-dependent (NDD)] and weight (<50 kg and ≥ 50 kg).

*Study Patients:*

The following were main inclusion criteria:

- Patients 2 to 20 years with CKD
- On stable PD or HD for at least 3 months or for NDD-CKD with GFR<60 mL/min/1.73 m2 for at least 3 months
- On stable EPO therapy (±25% of current dose) for ≥ 8 weeks
- Hemoglobin 11.0-13.5 g/dL, inclusive
- Ferrtin ≤ 800 ng/mL
- Transferrin saturation (TSAT) 20%-50%, inclusive.

*Study Treatment:*

Study subjects were randomized to one of the three following dosing groups:

- Venofer 0.5 mg/kg
- Venofer 1.0 mg/kg
- Venofer 2.0 mg/kg

The maximum single dose was 100 mg of elemental iron in all groups.

The HDD-CKD subjects received study drug once every 14 days (Day 0, Day 14, Day 28, Day 42, Day 56, and Day 70, for a total of 6 doses) over 12 week period.

The PDD or NDD-CKD subjects received study drug once every 28 days (Day 0, Day 28, and Day 56) for a total of 3 doses.

All doses of Venofer were administered either undiluted by IV push over 5 minutes or diluted in 25 mL of 0.9% Sodium Chloride, USP and administered over 5 to 60 minutes. For HD subjects, the dose was given within the first hour of dialysis.

The EPO dose, type, route, and frequency were to remain constant from consent to the end of study. The EPO doses were to be decreased for safety reasons only at the Investigator's discretion. No blood transfusions or additional iron preparations (including IV iron, oral iron, or multivitamns with iron) were allowed after randomization.

*Study Endpoints:*

Primary safety parameters: adverse events and laboratory evaluations

Secondary parameters: efficacy endpoint:

- Clinical success for a subject was defined as achieving, for the 12-week post-baseline period, the following criteria:
  - Hemoglobin between 10.5 g/dL and 14.0 g/dL, inclusive, and
  - TSAT between 20 and 50%, inclusive, and
  - Stable EPO dosing (±25% of baseline dose) or a decrease >25% in EPO dose).
- Occurrence of any hemoglobin > 14.0 g/dL post-baseline.
- Any change from baseline in hemoglobin ≥ 1.0 g/dL post-baseline.
- Occurrence of any TSAT < 20% post-baseline.
- Occurrence of any TSAT > 50% post-baseline.
- Change from baseline to highest hemoglobin post-baseline
- Change from baseline to highest ferritin post-baseline
- Change from baseline to highest TSAT post-baseline
- Change from baseline to highest reticulocyte count post-baseline

*Protocol Amendments*

There were three protocol amendments and the first two amendments occurred before the first patient was randomized in the study (October 24, 2005).

In Protocol Amendment #1 on December 23, 2004, the applicant modified the secondary endpoint of the study for efficacy from maintenance of hemoglobin within 10% of the baseline value to the following efficacy endpoints:

- "Clinical success" defined as subjects that maintain hemoglobin between 10.5-14.0g/dL inclusive and ferritin between 100-500ng/ml inclusive and stable erythropoietin dosing (+/- 10% of baseline dose) or a decrease more than 10% in dosing for the 12 week period.
- hemoglobin more than 14g/dL.
- TSAT < 20% and > 50%.
- ferritin more than 500ng/ml.

In Protocol Amendment #2 on August 15, 2005, the applicant proposed to include pediatric patients with non-dialysis dependent chronic kidney disease (NDD-CKD) who are on erythropoietin in addition to patients undergoing peritoneal dialysis (PD-CKD) or hemodialysis (HD-CKD). The major modifications to this protocol included:

- Increased the number of patients from 45 to 60 patients
- Enroll patients with NDD-CKD
- Modified Clinical success as hemoglobin between 10.5 g/dl - 14.0g/dL, TSAT between 20%-50% and stable erythropoietin dosing (+/- 25% of baseline dose) or a decrease more than 25% in erythropoietin dosing.

In Protocol Amendment #3 dated July 19, 2006 in response to the Agency's recommendations:

- Increased number of patients to 120 to collect sufficient safety data in pediatric patients
- Stratified patients to HD-CKD or PD-CKD or NDD-CKD at randomization

6.1.2 Demographics

The study randomized 145 patients and the mean age of subjects was 13 years with a median of 14-15 years, ranging from 2 to 20 years among the 3 Venofer dose groups. Over 70% of subjects were 12 years or older in all 3 groups. The following table shows the age group distribution in each Venofer dose group.

**Table 3. Age Group Distribution by Treatment Group in Randomized Patients**

| Age (years) | Venofer 0.5 mg/kg | Venofer 1.0 mg/kg | Venofer 2.0 mg/kg | Total |
|---|---|---|---|---|
| 2-5 | 3 | 4 | 3 | 10 (6.9%) |
| 6-11 | 10 | 9 | 12 | 31 (21.4%) |
| 12-17 | 26 | 27 | 28 | 81 (55.9%) |
| 18-20 | 10 | 7 | 6 | 23 (15.8%) |
| Total | 49 | 47 | 49 | 145 (100%) |

There were 84 males and 61 females in the study. The number of male subjects was slightly more than female subjects in all three groups. Over half of subjects were Caucasians in all groups. No significant differences were noted among the 3 Venofer dose groups for demographic characteristics (see table below).

**Table 4. Demographic Characteristics at Baseline (All Randomized Subjects)**

| Demographic | Venofer 0.5 mg/kg (N=49) | Venofer 1.0 mg/kg (N=47) | Venofer 2.0 mg/kg (N=49) |
|---|---|---|---|
| Age (years) | | | |
| Mean (SD) | 13.8 (4.40) | 13.1 (4.62) | 13.1 (4.87) |
| Median | 15.0 | 14.0 | 15.0 |
| Minimum- Maximum | 2,20 | 2,20 | 2,20 |
| Gender | | | |
| Male | 28 (57.1%) | 25 (53.2%) | 31 (63.3%) |
| Female | 21 (42.9%) | 22 (46.8%) | 18 (36.7%) |
| Race | | | |
| Caucasian | 29 (59.2%) | 24 (51.1%) | 31 (63.3%) |
| Black | 10 (20.4%) | 10 (21.3%) | 10 (20.4%) |
| Hispanic | 10 (20.4%) | 11 (23.4%) | 7 (14.3%) |
| Asian | 0 | 1 (2.1%) | 1 (2.0%) |
| Other | 0 | 1(2.1%) | 0 |
| Weight (kg) | | | |
| Mean (SD) | 45.2 (18.41) | 43.5 (22.93) | 42.5 (20.82) |
| Median | 43.7 | 40.6 | 42.0 |
| Minimum- Maximum | 11,90 | 10, 107 | 7, 104 |

| | | | |
|---|---|---|---|
| Height (cm) | | | |
| Mean (SD) | 145.9 (23.07) | 143.3 (23.66) | 142.6 (26.30) |
| Median | 146.0 | 149.2 | 150.0 |
| Minimum- Maximum | 88, 183 | 76, 176 | 69, 178 |

SD=standard deviation

No significant differences were noted in mean or median weight and height among the 3 Venofer dose groups.

Over 60% of subjects underwent hemodialysis and 25% underwent peritoneal dialysis in all three dose groups (see Table below). The mean baseline hemoglobin level in the study patients was 12 g/dL with mean TSAT of 33% and ferritin of 300 ng/mL.

**Table 5. Baseline Characteristics (All Randomized Subjects)**

| Baseline Characteristic | Venofer 0.5 mg/kg (N=49) | Venofer 1.0 mg/kg (N=47) | Venofer 2.0 mg/kg (N=49) |
|---|---|---|---|
| Dialysis method [n (%)] | | | |
| Hemodialysis | 31 (63.3%) | 30 (63.8%) | 30 (61.2%) |
| Peritoneal dialysis | 12 (24.5%) | 12 (25.5%) | 12 (24.5%) |
| Non-dialysis dependent | 6 (12.2%) | 5 (10.6%) | 7 (14.3%) |
| Hemoglobin (g/dL) [mean (SD)] | 12.2 (0.8) | 12.2 (0.9) | 12.0 (0.8) |
| Ferritin (ng/mL) [mean (SD)] | 262.2 (211.1) | 307.6 (266.8) | 325.8 (293.3) |
| TSAT (%) [mean (SD)] | 33.0 (10.2) | 33.2 (9.4) | 31.9 (9.5) |

SD=standard deviation

The most common medical history abnormalities reported among each dose group included genitourinary disorders, drug allergies, hematopoietic/lymphatic disorders, and cardiovascular disorders. About 25% of study patients had received IV iron products and 35% of patients had received oral iron products prior to the study. The types of medications received during the study were generally similar among the dose groups.

6.1.3 Subject Disposition

Of these 145 randomized patients, 2 each in 0.5 mg/kg (5 years [PD-CKD] and 12 years [HD-CKD])and 2.0 mg/kg [2 years [PD-CKD] and 15 years [PD-CKD])groups were discontinued from the study prior to dosing. Reasons for discontinuation were renal transplant (2 subjects), subject request (1 subject), and termination of study by sponsor (1 subject). These 4 subjects were excluded from the efficacy and safety analysis.

Among the 145 randomized patients, 120 (83%) completed the study. These included 41 (84%) patients in the 0.5 mg/kg group, 41 (87%) in the 1.0 mg/kg group, and 38 (78%) in the 2.0 mg/kg

group. Among the 25 (17%) subjects who did not complete the study, the most frequent reasons for discontinuation from the study were renal transplant (14 subjects, 9.7%) (see Table below).

**Table 6. Subject Disposition by Treatment groups**

| Subject Disposition | Venofer 0.5 mg/kg | Venofer 1.0 mg/kg | Venofer 2.0 mg/kg | Total |
|---|---|---|---|---|
| Randomized | 49 (100%) | 47 (100%) | 49 (100%) | 145 (100%) |
| Safety Population* | 47 (95.9%) | 47 (100%) | 47 (95.9%) | 141 (97.2%) |
| mITT Population** | 46 (93.9%) | 45 (95.7%) | 40 (81.6%) | 131 (90.3%) |
| Completed Study | 41 (83.7%) | 41 (87.2%) | 38 (77.6%) | 120 (82.8%) |
| Discontinued | 8 (16.3%) | 6 (12.8%) | 11 (22.4%) | 25 (17.2%) |
| Reasons for discontinuations | | | | |
| Renal transplant | 5 (62.5%) | 4 (66.7%) | 5 (45.5%) | 14 (56.0%) |
| EPO dosing increase >25% | 0 | 0 | 2 (18.2%) | 2 (8.0%) |
| Subject request | 0 | 0 | 1 (9.1%) | 1 (4.0%) |
| Adverse event | 0 | 0 | 1 (9.1%) | 1 (4.0%) |
| Investigator judgment | 0 | 0 | 1 (9.1%) | 1 (4.0%) |
| Lost to follow-up | 1 (12.5%) | 0 | 0 | 1 (4.0%) |
| Protocol violation | 1 (12.5%) | 0 | 0 | 1 (4.0%) |
| Termination by Sponsor | 1 (12.5%) | 0 | 0 | 1 (4.0%) |
| Use of IV iron outside of protocol | 0 | 1 (16.7%) | 0 | 1 (4.0%) |
| Hemoglobin <9.0 or >15.0 g/dL | 0 | 0 | 1 (9.1%) | 1 (4.0%) |
| Developed an exclusion criteria | 0 | 1 (16.7%) | 0 | 1 (4.0%) |

* Subjects who received at least 1 dose of study drug.

** All randomized subjects who received at least 1 dose of study drug, had a stable EPO dose for at least 8 weeks before randomization, and had at least 1 post-baseline hemoglobin and ferritin assessment.

Eight subjects had violations of inclusion/exclusion criteria (4 in 0.5 mg/kg, 1 in 1.0 mg/kg, and 3 in 2.0 mg/kg groups). Of these 8 subjects, 6 subjects (3 in 0.5 mg/kg, 1 in 1.0 mg/kg, and 2 in 2.0 mg/kg groups) were granted exceptions by the sponsor. The most common violations for which exception was granted were for inclusion criteria #5 (screening hemoglobin at central lab ≥ 11.0 to ≤ 13.5 g/dL) and #6 (Screening ferritin at central lab ≤ 800 ng/mL).

### 6.1.4 Analysis of Primary Endpoint(s)

The primary study parameters were the safety including adverse events and laboratory evaluation. Efficacy endpoints were considered as the secondary endpoints of the study.

A total of 131 subjects who received at least 1 dose of study drug, had a stable EPO dose for at least 8 weeks before randomization, and had at least 1 post-baseline hemoglobin and ferritin assessment were included in the Modified ITT (mITT) Population.

Clinical success is the pre-specified main efficacy endpoint for the study.

Clinical success was defined as achieving, for the 12-week post-baseline period, the following criteria:

- Hemoglobin between 10.5 g/dL and 14.0 g/dL, inclusive, and
- TSAT between 20 and 50%, inclusive, and
- Stable EPO dosing (± 25% of baseline dose) or a decrease > 25% in EPO dose

In an initial submission of this supplement, the study reported that the proportion of subjects who achieved clinical success was 89.1% in the 0.5 mg/kg group, 84.4% in the 1.0 mg/g group, and 87.5% in the 2.0 mg/kg group during the 12-week treatment period. There were no statistically significant differences among the three dose groups (see table below).

Discrepancies were identified for the rates of clinical success by the Agency and the applicant was requested to address this issue. The applicant later identified an error in the data analysis for clinical success. The numbers of clinical success initially reported were based on any time point but not entire 12 week treatment duration as defined in protocol.

**Table 7. Clinical Success at anytime during the 12-week period (mITT Population)**

| Efficacy Endpoint | Venofer 0.5 mg/kg (N=46) n (%) | Venofer 1.0 mg/kg (N=45) n (%) | Venofer 2.0 mg/kg (N=40) n (%) | Group Difference |
|---|---|---|---|---|
| Clinical Success | 41 (89.1%) | 38 (84.4%) | 35 (87.5%) | p>0.05 |
| Hemoglobin ≥ 10.5 g/dL and ≤14.0 | 45 (97.8%) | 42 (93.3%) | 38 (95.0%) | p>0.05 |
| TSAT ≥20% and ≤50% | 42 (91.3%) | 39 (86.7%) | 37 (92.5%) | p>0.05 |
| Stable EPO dosing | 46 (100.0%) | 45 (100.0%) | 39 (97.5%) | p>0.05 |

The applicant re-analyzed the clinical success endpoint, revised the study report and submitted as a major amendment to this supplement on April 27, 2012. A revised clinical success rate based on entire 12 week treatment period is presented in the table below. Only 20-30% subjects achieved clinical success over entire 3 months for all Venofer dosing groups. However, it is noted that about half of patients had maintained their hemoglobin between 10.5 g/dL and 14.0 g/dL over entire 3 months on a stable EPO dosing with the highest rate in the lowest dosing group (58.7% in 0.5 mg/kg, 46.7% in 1 mg/kg, and 45.0% in 2 mg/kg). TSAT maintenance (20-50%) showed a dose-response trend among the three Venofer dosing group (32.6% in 0.5 mg/kg, 40% in 1 mg/kg, and 50% in 2 mg/kg). Overall, no statistically significant differences in clinical success, hemoglobin and TSAT maintenance were found among the three Venofer dosing groups.

**Table 8. Clinical Success during the entire 12-week period (mITT Population) after re-analyzed data**

| Efficacy Endpoint | Venofer 0.5 mg/kg (N=46) n (%) | Venofer 1.0 mg/kg (N=45) n (%) | Venofer 2.0 mg/kg (N=40) n (%) | Group Difference |
|---|---|---|---|---|
| Clinical Success | 12 (26.1%) | 10 (22.2%) | 12 (30.0%) | p>0.05 |
| Hemoglobin ≥ 10.5 and ≤14.0 g/dL | 27 (58.7%) | 21 (46.7%) | 18 (45.0%) | p>0.05 |
| TSAT ≥20% and ≤50% | 15 (32.6%) | 18 (40.0%) | 20 (50.0%) | p>0.05 |
| Stable EPO dosing | 46 (100.0%) | 45 (100.0%) | 39 (97.5%) | p>0.05 |

The applicant also performed additional analysis for clinical success and its components at each assessment point as shown below. Clinical success rates at different assessment time points were 45-70% among the three dosing groups, which was higher than all visits during entire 3 month period.

**Table 9. Clinical success at assessment timepoints**

| Clinical Success | Venofer 0.5 mg/kg (N=46) n (%) | Venofer 1.0 mg/kg (N=45) n (%) | Venofer 2.0 mg/kg (N=40) n (%) | Group Difference |
|---|---|---|---|---|
| Day 28 | 32 (69.6%) | 30 (66.7%) | 12 (70.0%) | p>0.05 |
| Day 56 | 32 (69.6%) | 22 (48.9%) | 18 (55.0%) | p>0.05 |
| Day 84 | 25 (54.3%) | 23 (51.1%) | 20 (45.0%) | p>0.05 |
| All 3 visits | 12 (26.1%) | 10 (22.2%) | 39 (30.0%) | p>0.05 |

Proportion of patients with hemoglobin between 10.5 and 14.0 g/dL at different assessment timepoints were 62-94%, with the highest in the 0.5 mg/kg group. A statistically significant difference for hemoglobin maintenance was noted between the 0.5 mg/kg and the 1.0 mg/kg group at Day 28 and 56.

**Table 10. Hemoglobin between 10.5 and 14.0 g/dL at assessment timepoints**

| Hemoglobin between 10.5 and 14.0 g/dL | Venofer 0.5 mg/kg (N=46) n (%) | Venofer 1.0 mg/kg (N=45) n (%) | Venofer 2.0 mg/kg (N=40) n (%) | Group Difference |
|---|---|---|---|---|
| Day 28 | 43 (93.5%)* | 35 (77.8%) | 31 (77.5%) | *p=0.039 (vs. 1.0 mg/kg) |

| | | | | |
|---|---|---|---|---|
| Day 56 | 38 (82.6%)* | 28 (62.2%) | 30 (75.0%) | *p=0.036 (vs. 1.0 mg/kg) |
| Day 84 | 32 (69.6%) | 33 (73.3%) | 27 (67.5%) | p>0.05 |
| All 3 visits | 27 (58.7%) | 21 (46.7%) | 18 (45.0%) | p>0.05 |

Proportion of patients with TSAT between 20% and 50% at different assessment timepoints were 63-89%. No statistically significant differences were found among the three dosing groups.

**Table 11. TSAT between 20% and 50% at assessment timepoints**

| TSAT between 20% and 50% | Venofer 0.5 mg/kg (N=46) n (%) | Venofer 1.0 mg/kg (N=45) n (%) | Ve nofer 2.0 mg/kg (N=40) n (%) | Group Difference |
|---|---|---|---|---|
| Day 28 | 33 (71.7%) | 35 (77.8%) | 35 (87.5%) | P>0.05 |
| Day 56 | 36 (78.3%) | 31 (68.9%) | 25 (62.5%) | P>0.05 |
| Day 84 | 29 (63.0%) | 29 (64.4%) | 27 (67.5%) | p>0.05 |
| All 3 visits | 15 (32.6%) | 18 (40.0%) | 20 (50.0%) | p>0.05 |

6.1.5 Analysis of Secondary Endpoints(s)

The results of other efficacy analyses are shown below.

The proportion of subjects achieving an increase in hemoglobin ≥ 1.0 g/dL from baseline, hemoglobin > 14.0 g/dL, TSAT < 20%, or TSAT > 50% at anytime post-baseline is presented in the table below. No statistically significant differences were observed among the Venofer 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg dose groups for these secondary efficacy endpoints.

**Table 12. Other Efficacy Endpoints of the Study at Anytime Post-baseline (mITT Population)**

| Endpoints | Venofer 0.5 mg/kg (N=46) n (%) | Venofer 1.0 mg/kg (N=45) n (%) | Venofer 2.0 mglkg (N=40) n (%) | Group Difference |
|---|---|---|---|---|
| Hemoglobin increase ≥1.0 g/dL | 14 (30.4%) | 10 (22.2%) | 14 (35.0%) | p>0.05 |
| Hemoglobin >14.0 g/dL | 3 (6.5%) | 4 (8.9%) | 4 (10.0%) | p>0.05 |
| TSAT <20% | 16 (34.8%) | 13 (28.9%) | 8 (20.0%) | p>0.05 |
| TSAT >50% | 11 (23.9%) | 7 (15.6%) | 8 (20.0%) | p>0.05 |

There were no statistically significant differences between any two groups for the mean change from baseline to highest post-baseline value in hemoglobin, ferritin, TSAT, and reticulocytes except for mean changes in TSAT from baseline to highest post-baseline value between the 1.0 mg/kg and 2.0 mg/g dose groups (p = 0.0457). See Table below.

**Table 13. Mean Change in Hemoglobin, Ferritin, TSAT, and Reticulocytes from Baseline to Highest Post-baseline (mITT Population)**

| | Venofer 0.5 mg/kg (N=46) | Venofer 1.0 mg/kg (N=45) | Venofer 2.0 mg/kg (N=40) | Group Difference |
|---|---|---|---|---|
| Hemoglobin (g/dL) | 0.32 | 0.25 | 0.61 | p>0.05 |
| Ferritin (ng/mL) | 2.60 | 33.08 | 62.73 | p>0.05 |
| TSAT(%) | 8.07 | 5.62 | 13.73 | 1.0 mg/kg vs. 2.0 mg/kg P=0.0457<br>Other comparisons p>0.05 |
| Reticulocytes (%) | 0.27 | 0.31 | 0.47 | p>0.05 |

No clinically notable differences were observed for the proportion of subjects with highest hemoglobin, ferritin, TSAT, and reticulocytes value by visit.

6.1.6 Other Endpoints

*Iron indices*

No statistically significant differences were observed among the Venofer 0.5 mg/kg, 1.0 mg/kg, or Venofer 2.0 mg/kg dose groups for any of the iron indices assessed. The mean changes from baseline to Week 12 were generally small and not considered clinically meaningful.

**Table 14. Mean Changes From Baseline to Week 12 in Iron Indices (All Safety Subjects)**

| Iron Indices (Units) | Venofer 0.5 mg/kg (N=47) | | Venofer 1.0 mg/kg (N=47) | | Venofer 2.0 mg/kg (N=47) | | p-value |
|---|---|---|---|---|---|---|---|
| Serum Iron (ug/dL) | N | | N | | N | | |
| Baseline Mean (SD) | 47 | 78.8 (25.17) | 47 | 74.9 (28.82) | 47 | 70.1 (21.76) | |
| Mean Change to Week 12 (SD) | 36 | 0.1 (29.04) | 39 | -5.1 (45.52) | 38 | 3.1 (35.17) | 0.90 |
| TIBC (ug/dL) | N | | N | | N | | |
| Baseline Mean (SD) | 47 | 242.2 (48.85) | 47 | 225.8 (57.10) | 47 | 223.0 (49.28) | |
| Mean Change to Week 12 (SD) | 36 | -8.4 (30.85) | 39 | -2.1 (35.88) | 38 | -11.3 (34.23) | 0.41 |
| TSAT(%) | N | | N | | N | | |
| Baseline Mean (SD) | 47 | 33.0 (10.16) | 47 | 33.2 (9.38) | 47 | 31.9 (9.50) | |
| Mean Change to Week 12 (SD) | 36 | 2.0 (13.49) | 39 | -1.6 (17.71) | 38 | 2.6 (16.73) | 0.81 |

| Ferritin (ng/mL) | N | | N | | N | | |
|---|---|---|---|---|---|---|---|
| Baseline Mean (SD) | 24 | 262.2 (211.0) | 31 | 307.6 (266.8) | 24 | 325.8 (293.3) | |
| Mean Change to Week 12 (SD) | 18 | -30.8 ( 111.5) | 25 | -24.8 (158.2) | 17 | -15.0 (147.9) | 0.72 |

6.1.7 Subpopulations

An ad hoc subgroup analysis of the mean change from baseline to highest post-baseline values for hemoglobin and ferritin was performed comparing the subjects who were HDD (receiving 6 doses of study drug) vs. those who were non-HDD (receiving 3 doses of study drug). There was no significant difference. In subjects with HDD-CKD, there was a trend toward higher hemoglobin and ferritin at the higher doses. A summary of the mean change in hemoglobin and ferritin from baseline to highest post-baseline value is presented for HDD and non-HDD subjects in Table below.

**Table 15. Mean Change in Hemoglobin and Ferritin from Baseline to Highest Post-baseline Value for HDD and N on-HDD Subjects (mITT Population)**

| | Venofer 0.5 mg/kg | Venofer 1.0 mg/kg | Venofer 2.0 mg/kg | Group Difference |
|---|---|---|---|---|
| HDD Subjects | (N=29) | (N=29) | (N=24) | |
| Hemoglobin (g/dL) | 0.15 | 0.49 | 0.69 | p>0.05 |
| Ferritin (ng/mL) | -15.83 | 19.34 | 54.65 | p>0.05 |
| Non-HDD Subjects | (N=17) | (N=16) | (N=16) | |
| Hemoglobin (g/dL) | 0.64 | -0.17 | 0.49 | p>0.05 |
| Ferritin (ng/mL) | 68.94 | 118.98 | 108.53 | p>0.05 |

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Three different dosing regimens were studied in 1VEN03017.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No specific studies were conducted to evaluate the tolerance effect.

6.1.10 Additional Efficacy Issues/Analyses

None.

**Reviewer's Comments:**

Study 1VEN03017 failed to demonstrate a dose response relationship among the three Venofer dosing groups for the pre-specified efficacy endpoint of "clinical success". However, the study did show that about 40-50% of study patients maintained hemoglobin over entire 3 month treatment period with a stable ESA dose in all three Venofer dose groups. The Venofer 0.5 mg/kg group had the highest rate (58%) of hemoglobin maintenance among the three groups. Since the study was not conducted in patients with iron deficiency anemia (due to insufficient number of pediatric patients available to study), the results are limited to continuous maintenance treatment for 3 months to maintain iron status in pediatric patients who are on ESA therapy.

## 7 Review of Safety

***Safety Summary***

A total of 141 pediatric patients received at least one dose of Venofer in the study. These included 8 patients in age 2-5 years, 31 patients in age 6-11 years and 79 patients at age 12-17 years. There were 82 males and 59 females. The safety population included 90 patients with HD-CKD, 33 patients with PD-CKD and 18 patients on NDD-CKD. The total dose of Venofer administered was 112.3 mg in the 0.5 mg/kg group, 207.9 mg in the 1.0 mg/kg group, and 332.7 mg in the 2.0 mg/kg group over 12 week period.

No death was reported in the study. Twenty-five (17.7%) patients experienced at least one serious adverse event (SAE) in the study. More SAEs were reported in the higher dose groups as compared to the lowest dose groups: 5 (10.6%) subjects in the 0.5 mg/g group, 10 (21.3%) subjects in the 1.0 mg/kg group, and 10 (21.3%) subjects in the 2.0 mg/kg group. The most frequently reported SAEs included renal transplant, peritonitis, arteriovenous graft thrombosis, and hypertension. No SAEs were considered to be related to Venofer treatment.

Three patients prematurely discontinued Venofer treatment in the study including two due to renal transplant and one due to hyperparathyroidism and hypocalcemia. None was considered to be related to the study drug.

Seventy-eight (55%) subjects experienced at least one treatment-emergent adverse event (AE) in the study. A similar rate of treatment-emergent AEs was reported among the three Venofer dose groups: 57.4% (27/47) in the 0.5 mg/g group, 53.2% (25/47) in the 1.0 mg/kg group, and 55.3% (26/47) in the 2.0 mg/kg group. The most common treatment-emergent AEs (> 2% of patients) in all patient groups were headache (5.7%), respiratory tract viral infection (4.3%), peritonitis (3.5%), vomiting (3.5%), pyrexia (3.5%), dizziness (3.5%), cough (3.5%), renal transplant (3.5%), nausea (2.8%), arteriovenous fistula thrombosis (2.1%), hypotension (2.1%), and hypertension (2.1%). Adverse events that were considered to be drug-related treatment-emergent adverse events were reported in none of the patients in the Venofer 0.5 mg/kg group, in three patients each (6.4%) in the Venofer 1.0 mg/kg and 2.0 mg/kg groups. These drug-related

treatment-emergent adverse events included rash, vessel puncture site bruise, vomiting, feeling hot, blood pressure increased, dysgeusia, nausea, blood pressure decreased, and dizziness.

No serious hypersensitivity reactions were reported in the study. One subject (0.7%) in the 1.0 mg/kg group experienced Grade 1 rash that was considered to be a hypersensitivity/allergic reaction and to be related to the study drug. Additional 5 subjects (3.5%, 2 each in 0.5 mg/kg and 2.0 mg/kg, one in 1.0 mg/kg) experienced dermatitis, cold sweat, generalized pruritus, or skin irritation that was considered as potentially hypersensitivity/allergic reactions. Two patients (1.4%, one each in the 0.5 mg/kg group and the 1.0 mg/kg group) experienced hypotension events during the study, which were considered by the Investigator to be Grade 1 or 2 in severity and not related or unlikely related to study drug.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study 1VEN03017 was used to evaluate safety in pediatric population.

### 7.1.2 Categorization of Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) terminology was used to classify all adverse events with respect to System Organ Class (SOC) and preferred term in clinical trial.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Only one trial was submitted.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 141 pediatric patients received Venofer. These included 8 patients in age 2-5 years, 31 patients in age 6-11 years and 79 patients at age 12-17 years. The age distribution by treatment group is shown below. It included 90 patients with HD-CKD, 33 patients with PD-CKD and 18 patients on NDD-CKD.

**Table 16. Age Group Distribution by Treatment Group in Safety population**

| Age (years) | Venofer 0.5 mg/kg | Venofer 1.0 mg/kg | Venofer 2.0 mg/kg | Total |
|---|---|---|---|---|
| 2-5 | 2 | 4 | 2 | 8 (6.9%) |

| | | | | |
|---|---|---|---|---|
| 6-11 | 10 | 9 | 12 | 31 (21.4%) |
| 12-17 | 25 | 27 | 27 | 79 (55.9%) |
| 18-20 | 10 | 7 | 6 | 23 (15.8%) |
| Total | 47 | 47 | 47 | 141 (100%) |

The exposure, calculated as the total dose of Venofer administered, was 112.3 mg in the 0.5 mg/kg group, 207.9 mg in the 1.0 mg/kg group, and 332.7 mg in the 2.0 mg/kg group over 12 week period. See Table below for median and range of exposure.

**Table 17. Overall Exposure by Treatment Group**

| Total Dose (mg) | Venofer 0.5 mg/kg N=47 | Venofer 1.0 mg/kg N=47 | Venofer 2.0 mg/kg N=47 | Total (N=141) |
|---|---|---|---|---|
| Mean(SD) | 112.3 (56.7) | 207.9 (134.6) | 332.7 (162.1) | 217.6 (154.4) |
| Median | 108 | 210 | 300 | 189 |
| Min. - Max. | 17, 239 | 30, 600 | 42, 600 | 17, 600 |

SD=standard deviation

See Section 6.1.2 for demographics of the study population.

7.2.2 Explorations for Dose Response

See section 7.2.1 for doses studied in 1VEN03017.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or in vitro testing was performed.

7.2.4 Routine Clinical Testing

Routine clinical testing of clinical trials is adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

A single dose pharmacokinetic (PK) study in pediatric patients 12 to 16 years of age with NDD-CKD was conducted in response to PMC. Patients were treated with a single intravenous Venofer dose of 7 mg/kg with the maximum dose of 200 mg. Eleven patients were enrolled and 9 patients had pharmacokinetic data. The submitted PK results showed that female children have lower Cmax (36%) and longer half life (46%) than males. When comparing pediatric PK data with adult PK data, children appear to have higher dose adjusted Cmax and AUC than adults.

Compared to the referenced adult PK data in the original NDA, the Cmax and AUC of total serum iron were 1.42- and 1.67-fold higher, respectively. However, these findings were limited to a relatively small sample size and it is unclear if comparable analytical methods were used between adults and children (see FDA Clinical Pharmacology Review, Dr. Bahru A Habtemariam, Pharm.D., dated 4/8/2011). No pharmacokinetic information for pediatric patients younger than 12 years of age.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Hypersensitivity/anaphylactic-type reactions and hypotension adverse events were collected in the study.

## 7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in the study.

7.3.2 Nonfatal Serious Adverse Events

Twenty-five (17.7%) subjects experienced at least one serious adverse event (SAE) in the study (see Table below). More SAEs were reported in the higher dose groups as compared to the lowest dose groups: 5 (10.6%) subjects in the 0.5 mg/g group, 10 (21.3%) subjects in the 1.0 mg/kg group, and 10 (21.3%) subjects in the 2.0 mg/kg group (14 SAEs). The most frequently reported SAEs included renal transplant, peritonitis, arteriovenous graft thrombosis, and hypertension. Other SAEs reported in a single subject included appendicitis in 0.5 mg/kg group; pericardial effusion, supraventricular tachycardia, arteriovenous fistula thrombosis, hypocalcemia, and fecaloma in the 1.0 mg/kg group; and enterobacter bacteremia, subdural hematoma, azotemia, clavicle fracture, pyrexia, ventricular arrhythmia, hypertensive encephalopathy, and hyperparathyroidism in the 2.0 mg/kg group. No SAEs were considered by the Investigator to be related to study drug.

**Table 18. Serious Adverse Events Reported in ≥ 2 Subjects in the Study**

| SAEs | Venofer 0.5 mg/kg N=47 | Venofer 1.0 mg/kg N=47 | Venofer 2.0 mg/kg N=47 | Total (N=141) |
|---|---|---|---|---|
| Subject with at least 1 SAE | 5 (10.6%) | 10 (21.3%) | 10 (21.3%) | 25 (17.7%) |
| Renal Transplant | 3 (6.4%) | 1 (2.1%) | 1 (2.1%) | 5 (3.5%) |
| Peritonitis | 0 | 3 (6.4%) | 0 | 3 (2.1%) |
| Hypertension | 0 | 0 | 3 (6.4%) | 3 (2.1%) |
| Arteriovenous graft thrombosis | 1 (2.1%) | 0 | 2 (4.3%) | 3 (2.1%) |

Note: one subject may report more than 1 event.

7.3.3 Dropouts and/or Discontinuations

Three subjects, 1 in each dose group, were prematurely discontinued from study drug due to the occurrence of adverse events. Two subjects underwent renal transplant and one subject (in 2.0 mg/kg group) experienced Grade 2 hyperparathyroidism on Study Day 49 and hypocalcemia on Study Day 63. Each of these events was considered by the Investigator to be not related to study drug.

7.3.4 Significant Adverse Events

*Potential Hypersensitivity/Allergic Reactions*

No subject experienced a serious hypersensitivity reaction. One subject (0.7%) in the 1.0 mg/kg group experienced Grade 1 rash that was considered to be a hypersensitivity/allergic reaction. Additional 5 subjects (3.5%, 2 each in 0.5 mg/kg and 2.0 mg/kg groups and 1 in the 1.0 mg/kg group) experienced treatment-emergent adverse events associated with Skin and Subcutaneous Tissue Disorders, including dermatitis atopic and cold sweat in the 0.5 mg/kg group, generalized pruritus in the 1.0 mg/kg group, and skin irritation and allergic dermatitis in the 2.0 mg/kg group. Each of these events was classified by the Investigator as Grade 1 in severity. The only event considered related to study drug by the Investigator was rash in one subject in the 1.0 mg/kg group.

*Hypotension*

Two subjects (1.4%, one each in the 0.5 mg/kg group and the 1.0 mg/kg group) were reported as having hypotension during the study. Each of these events of hypotension was considered by the Investigator to be Grade 1 or Grade 2 in severity and not related or unlikely related to study drug. Neither of these subjects had a history of hypotension.

7.3.5 Submission Specific Primary Safety Concerns

None.

**7.4 Supportive Safety Results**

7.4.1 Common Adverse Events

Seventy-eight (55%) subjects experienced at least one treatment-emergent adverse event in the study. There were similar rates of AEs reported among the three dose groups: 57.4% (27/47) in the 0.5 mg/g group, 53.2% (25/47) in the 1.0 mg/kg group, and 55.3% (26/47) in the 2.0 mg/kg group.

The most common treatment-emergent adverse events (AEs) (> 2% of subjects) in all patients were headache (5.7%), respiratory tract viral infection (4.3%), peritonitis (3.5%), vomiting (3.5%), pyrexia (3.5%), dizziness (3.5%), cough (3.5%), renal transplant (3.5%), nausea (2.8%), Arteriovenous fistula thrombosis (2.1%), hypotension (2.1%), and hypertension (2.1%).

There are no significant differences in the frequency of common AEs noted among the three Venofer dose groups.

A summary of treatment-emergent adverse events experienced by ≥ 2 subjects in any of the Venofer dose groups during the study is presented in Table below.

**Table 19. Treatment-Emergent Adverse Events Experienced by ≥ 2 Subjects in Any Venofer Dose Groups (Safety Population)**

| System Organ Class<br>Preferred Term | Venofer 0.5 mg/kg (N=47) | Venofer 1.0 mg/kg (N=47) | Venofer 2.0 mg/kg (N=47) | Total (N=141) N (%) |
|---|---|---|---|---|
| At least 1 Treatment-Emergent Adverse | 27 (57.4%) | 25 (53.2%) | 26(55.3%) | 78 (55.3%) |
| Cardiac disorders | 2 (4.3%) | 3 (6.4%) | 1 (2.1%) | 6 (4.3%) |
| Tachycardia | 2 (4.3%) | 0 | 0 | 2 (1.4%) |
| Gastrointestinal Disorders | 6 (12.8%) | 9 (19.1%) | 6 (12.8) | 21 (14.9%) |
| Vomiting | 1 (2.1%) | 3 (6.4%) | 1 (2.1%) | 5 (3.5%) |
| Peritonitis | 0 | 3 (6.4%) | 2 (4.3%) | 5 (3.5%) |
| Nausea | 1 (2.1%) | 1 (2.1%) | 2 (4.3%) | 4 (2.8%) |
| General disorders and administration site conditions | 5 (10.6%) | 5 (10.6%) | 3 (6.4%) | 13 (9.2%) |
| Pyrexia | 2 (4.3%) | 2 (4.3%) | 1 (2.1%) | 5 (3.5%) |
| Infections and Infenfestations | 10 (21.3%) | 9 (19.1%) | 7 (14.9%) | 26 (18.4%) |
| Upper respiratory tract infection | 0 | 3 (6.4%) | 0 | 3 (2.1%) |
| Respiratory tract infection viral | 4 (8.5%) | 0 | 2 (4.3%) | 6 (4.3%) |
| Urinary tract infection | 2 (4.3%) | 0 | 0 | 2 (1.4%) |
| Otitis media | 0 | 2 (4.3%) | 0 | 2 (1.4%) |
| Injury, poisoning and procedural complications | 4 (8.5%) | 3 (6.4%) | 5 (10.6%) | 12 (8.5%) |
| Arteriovenous fistula thrombosis | 1 (2.1%) | 2 (4.3%) | 0 | 3 (2.1%) |
| Investigation | 2 (4.3%) | 0 | 4 (8.5%) | 6 (4.3%) |
| Blood pressure increased | 2 (4.3%) | 0 | 3 (6.4%) | 5 (3.5%) |
| Nervous System Disorders | 5 (10.6%) | 5(10.6%) | 7 (14.9%) | 17 (12.1%) |
| Headache | 2 (4.3%) | 4 (8.5%) | 2 (4.3%) | 8 (5.7%) |
| Dizziness | 2 (4.3%) | 1 (2.1%) | 2 (4.3%) | 5 (3.5%) |
| Dysgeusia | 0 | 0 | 2 (4.3%) | 2 (1.4%) |

| | | | | |
|---|---|---|---|---|
| Respiratory, Thoracic and Mediastinal Disorders | 3 (6.4%) | 1 (2.1%) | 3 (6.4%) | 7 (5.0%) |
| Cough | 1 (2.1%) | 1 (2.1%) | 3 (6.4%) | 5 (3.5%) |
| Surgical and Medical Procedures | 3 (6.4%) | 1 (2.1%) | 1 (2.1%) | 5 (3.5%) |
| Renal transplant | 3 (6.4%) | 1 (2.1%) | 1 (2.1%) | 5 (3.5%) |
| Vascular disorders | 4 (8.5%) | 1 (2.1%) | 2 (4.3%) | 7 (5.0%) |
| Hypotension | 2 (4.3%) | 1 (2.1%) | 0 | 3 (2.1%) |
| Hypertension | 1 (2.1%) | 0 | 2 (4.3%) | 3 (2.1%) |

*Drug-Related Treatment-Emergent Adverse Events*

During the study, at least 1 drug-related treatment-emergent adverse event (defined as possibly or probably related) was experienced by 0.0% (0/47) of the subjects in the Venofer 0.5 mg/kg group, 6.4% (3/47) of the subjects in the Venofer 1.0 mg/kg group, and 6.4% (3/47) of the subjects in the Venofer 2.0 mg/kg group (See table below). These drug-related treatment-emergent adverse events included rash, vessel puncture site bruise, vomiting, feeling hot, blood pressure increased, dysgeusia, nausea, blood pressure decreased, and dizziness.

**Table 19. Drug-related Treatment-Emergent Adverse Events Experienced in Any Venofer Dose Groups (Safety Population)**

| Related AEs | Venofer 0.5 mg/kg N=47 | Venofer 1.0 mg/kg N=47 | Venofer 2.0 mg/kg N=47 | Total (N=141) |
|---|---|---|---|---|
| Subject with at least 1 related AE | 0 | 3 (6.4%) | 3 (6.4%) | 6 (4.2%) |
| Rash | 0 | 1 (2.1%) | 0 | 1 (0.7%) |
| Vessel puncture site bruise | 0 | 1 (2.1%) | 0 | 1 (0.7%) |
| Vomiting | 0 | 1 | 0 | 1 (0.7%) |
| Feeling hot | 0 | 0 | 1 (2.1%) | 1 (0.7%) |
| Blood pressure increased | 0 | 0 | 1 (2.1%) | 1 (0.7%) |
| dysgeusia | 0 | 0 | 2 (4.2%) | 2 (1.4%) |
| Nausea | 0 | 0 | 2 (4.2%) | 2 (1.4%) |
| Blood pressure decreased | 0 | 0 | 1 (2.1%) | 1 (0.7%) |
| Dizziness | 0 | 0 | 1 (2.1%) | 1 (0.7%) |

7.4.2 Laboratory Findings

*Hematology*

Two (4.3%) subjects in the Venofer 1.0 mg/kg group were reported as having treatment-emergent abnormal hemoglobin values, 2 (4.3%) subjects in the Venofer 2.0 mg/kg group were

reported as having treatment-emergent abnormal neutrophils, and 1 (2.1%) subject in the Venofer 2.0 mg/g group was reported as having treatment-emergent abnormal platelets.

No significant difference in hematogical parameters among three treatment groups except for MCHC was observed for mean change from baseline to Week 12 (see Table below).

**Table 20. Hematology Laboratory Parameters (Safety Population)**

| Chemistry Parameter (Units) | Venofer 0.5 mglkg (N=47) | | Venofer 1.0 mg/kg (N=47) | | Venofer 2.0 mglkg (N=47) | | p-value |
|---|---|---|---|---|---|---|---|
| Hematocrit(%) | N | | N | | N | | |
| Baseline Mean (SD) | 44 | 37.0 (3.16) | 47 | 37.3 (3.24) | 45 | 36.8 (2.66) | |
| Mean Change to Week 12 (SD) | 33 | -1.8 (3.97) | 35 | -1.3 (5.82) | 33 | -0.5 (5.78) | 0.2903 |
| MCV(fL) | | | | | | | |
| Baseline Mean (SD) | 44 | 89.3 (5.01) | 46 | 88.8 (7.52) | 43 | 89.0 (6.86) | |
| Mean Change to Week 12 (SD) | 33 | -0.9 (3.72) | 35 | 0.5 (3.73) | 33 | 1.4 (4.76) | 0.0845 |
| MCH (pg) | | | | | | | |
| Baseline Mean (SD) | 44 | 29.7 (1.93) | 46 | 29.1 (2.34) | 43 | 29.4 (2.12) | 0.263 |
| Mean Change to Week 12 (SD) | 33 | 0.1 (1.17) | 35 | 0.0 (1.15) | 33 | 0.4 (0.99) | |
| MCHC(g/dL) | | | | | | | |
| Baseline Mean (SD) | 44 | 33.2 (1.49) | 46 | 32.8 (1.44) | 43 | 33.0 (1.49) | |
| Mean Change to Week 12 (SD) | 33 | 0.4 (1.22) | 35 | -0.3 (1.35) | 33 | 0.0 (1.99) | 0.039 |
| Platelets ($10^3/\mu L$) | | | | | | | |
| Baseline Mean (SD) | 42 | 244.9 (55.80) | 46 | 263.0 (84.37) | 42 | 227.6 (68.57) | |
| Mean Change to Week 12 (SD) | 31 | -9.6 (41.58) | 34 | 1.6 (58.63) | 31 | -10.3 (61.38) | 0.389 |
| Reticulocytes (%) | | | | | | | |
| Baseline Mean (SD) | 31 | 2.14 (0.865) | 38 | 1.97 (0.549) | 29 | 1.95 (0.767) | |
| Mean Change to Week 12 (SD) | 24 | -0.15 (0.669) | 29 | 0.03 (0.650) | 21 | 0.15 (0.781) | 0.461 |
| CH-R (pg) | N | | N | | N | | |
| Baseline Mean (SD) | 44 | 31.58 (1.999) | 46 | 31.30 (2.117) | 44 | 31.38 (2.226) | |
| Mean Change to Week 12 (SD) | 33 | 0.32 (1.484) | 35 | -0.18 (1.458) | 33 | 0.25 (1.873) | 0.259 |
| RBC ($10^6/\mu L$) | N | | N | | N | | |
| Baseline Mean (SD) | 44 | 4.16 (0.394) | 46 | 4.22 (0.512) | 43 | 4.16 (0.402) | |
| Mean Change to Week 12 (SD) | 33 | -0.17 (0.501) | 35 | -0.17 (0.623) | 33 | -0.13 (0.585) | 0.759 |
| WBC ($10^3/\mu L$) | N | | N | | N | | |
| Baseline Mean (SD) | 44 | 6.99 (2.59) | 46 | 7.11 (2.13) | 43 | 6.66 (2.10) | |
| Mean Change to Week 12 (SD) | 33 | | 35 | | 33 | -0.09 (2.00) | 0.298 |
| Neutrophils (%) | N | | N | | N | | |
| Baseline Mean (SD) | 44 | 56.08 (11.68) | 46 | 51.90(12.14) | 43 | 53.46 (9.90) | |
| Mean Change to Week 12 (SD) | 33 | -1.94 (11.80) | 35 | 3.55 (11.27) | 33 | -0.99 (8.10) | 0.230 |
| Lymphocytes (%) | N | | N | | N | | |
| Baseline Mean (SD) | 44 | 33.77 (9.90) | 46 | 37.27 (11.89) | 43 | 35.84 (8.80) | |
| Mean Change to Week 12 (SD) | 33 | 1.08 (10.68) | 35 | -2.17 (9.15) | 33 | 1.41 (7.39) | 0.417 |
| Monocytes (%) | N | | N | | N | | |
| Baseline Mean (SD) | 44 | 5.24 (1.94) | 46 | 5.10 (1.36) | 43 | 5.73 (1.93) | |
| Mean Change to Week 12 (SD) | 33 | 0.35 (2.25) | 35 | -0.20 (2.18) | 33 | 0.50 (1.92) | 0.051 |
| Basophils (%) | N | | N | | N | | |
| Baseline Mean (SD) | 44 | 0.81 (0.51) | 46 | 0.87 (0.57) | 43 | 0.73 (0.38) | |
| Mean Change to Week 12 (SD) | 33 | 0.14 (0.67) | 35 | -0.14 (0.80) | 33 | -0.01 (0.51) | 0.441 |
| Eosinophils (%) | N | | N | | N | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Baseline Mean (SD) | 44 | 4.05 (2.71) | 46 | 4.78 (3.69) | 43 | 4.19 (2.91) | |
| Mean Change to Week 12 (SD) | 33 | 0.21 (1.79) | 35 | -0.93 (2.81) | 33 | -0.94 (2.33) | 0.086 |

*Chemistry*

One (2.1 %) subject in the Venofer 1.0 mg/kg group was reported as having treatment-emergent abnormal alkaline phosphatase and albumin values.

A summary of mean changes from baseline to Week 12 in chemistry parameters is presented in Table below. No significant differences were observed among the three Venofer dose groups for any of the chemistry parameters assessed.

**Table 21. Mean Changes from Baseline to Week 12 in Chemistry Laboratory Parameters (Safety Population)**

| Chemistry Parameter (Units) | Venofer 0.5 mglkg (N=47) | | Venofer 1.0 mg/kg (N=47) | | Venofer 2.0 mglkg (N=47) | | p-value |
|---|---|---|---|---|---|---|---|
| BUN (mg/dL) | N | | N | | N | | |
| Baseline Mean (SD) | 44 | 49.3 (16.87) | 47 | 51.5 (20.65) | 45 | 58.1 (19.84) | |
| Mean Change to Week 12 (SD) | 33 | 5.7 (21.19) | 36 | 3.6 (24.09) | 35 | 1.6 (19.54) | 0.9939 |
| Creatinine (mg/dL) | | | | | | | |
| Baseline Mean (SD) | 44 | 8.12 (4.293) | 47 | 8.65 (4.531) | 45 | 8.43 (3.691) | |
| Mean Change to Week 12 (SD) | 33 | 0.66 (2.090) | 36 | -0.09 (2.583) | 35 | 0.27 (I .972) | 0.3856 |
| Serum Potassium (mEq/L) | | | | | | | |
| Baseline Mean (SD) | 44 | 4.55 (0.730) | 46 | 4.62 (0.679) | 43 | 4.82 (0.984) | |
| Mean Change to Week 12 (SD) | 33 | -0.18 (0.611) | 35 | -0.06 (0.681) | 32 | 0.03 (0.993) | 0.2408 |
| Chloride (mEq/L) | | | | | | | |
| Baseline Mean (SD) | 44 | 101.6 (4.71) | 47 | 100.5 (4.85) | 45 | 100.2 (5.46) | |
| Mean Change to Week 12 (SD) | 33 | -0.5 (4.13) | 36 | 0.0 (3.76) | 35 | -0.1 (4.58) | 0.9784 |
| Bicarbonate (mEq/L) | | | | | | | |
| Baseline Mean (SD) | 44 | 20.07 (3.777) | 47 | 20.83 (3.887) | 44 | 21.25 (3.682) | |
| Mean Change to Week 12 (SD) | 33 | -0.05 (4.334) | 36 | -0.57 (3.918) | 35 | -0.46 (4.099) | 0.9625 |
| Calcium (mg/dL) | | | | | | | |
| Baseline Mean (SD) | 44 | 9.81 (0.991) | 47 | 9.87 (0.825) | 45 | 9.79 (1.177) | |
| Mean Change to Week 12 (SD) | 33 | -0.27 (0.719) | 36 | -0.16 (0.741) | 35 | -0.09 (1.234) | 0.7170 |
| Phosphorus (mg/dL) | | | | | | | |
| Baseline Mean (SD) | 44 | 5.86 (1.791) | 46 | 5.97 (1.960) | 43 | 6.13 (1.937) | |
| Mean Change to Week 12 (SD) | 33 | 0.22 (1.877) | 35 | 0.12 (1.943) | 32 | -0.13 (1.738) | 0.7169 |
| Alkaline Phosphatase (U/L) | | | | | | | |
| Baseline Mean (SD) | 44 | 217.1 (162.83) | 47 | 295.1 (269.54) | 45 | 334.4 (414.01) | |
| Mean Change to Week 12 (SD) | 33 | 3.5 (99.32) | 36 | 33.6 (211.94) | 35 | -58.5 (290.71) | 0.2639 |
| AST (SGOT) (U/L) | | | | | | | |
| Baseline Mean (SD) | 43 | 20.7 (9.64) | 44 | 22.9 (11.52) | 43 | 21.8 (12.83) | |
| Mean Change to Week 12 (SD) | 31 | -1.9 (7.95) | 33 | 0.2 (14.86) | 34 | -2.7 (9.54) | 0.4113 |
| Lactic Dehydrogenase (U/L) | | | | | | | |
| Baseline Mean (SD) | 41 | 194.3 (53.20) | 44 | 195.1 (53.28) | 43 | 175.3 (39.42) | |
| Mean Change to Week 12 (SD) | 32 | 0.0 (38.19) | 33 | 0.8 (35.84) | 32 | -5.2 (40.83) | 0.4876 |
| Albumin (g/dL) | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Baseline Mean (SD) | 44 | 3.96 (0.534) | 47 | 3.74 (0.529) | 44 | 3.78 (0.417) | |
| Mean Change to Week 12 (SD) | 33 | -0.16 (0.339) | 36 | -0.07 (0.361) | 35 | -0.04 (0.393) | 0.6071 |

7.4.3 Vital Signs

Changes from baseline to Weeks 2, 4, 6, 8, 10, and 12 prior to dosing to 10 and 20 minutes post-dosing for systolic blood pressure, diastolic blood pressure, heart rate, and temperature were generally small and not considered clinically meaningful for each of the Venofer dose groups.

7.4.4 Electrocardiograms (ECGs)

Not performed.

7.4.5 Special Safety Studies/Clinical Trials

Not performed.

7.4.6 Immunogenicity

N/A

## 7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Treatment-emergent serious adverse events and drug-related adverse events were reported more frequent in the Venofer 1.0 mg/kg and 2.0 mg/kg group than the 0.5 mg/kg group.

7.5.2 Time Dependency for Adverse Events

Hypersensitivity and hypotension reaction were experienced shortly (within 30 minutes in most cases) after Venofer administration.

7.5.3 Drug-Demographic Interactions

No identified.

7.5.4 Drug-Disease Interactions

Not identified.

7.5.5 Drug-Drug Interactions

Not performed.

## 7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not performed.

7.6.2 Human Reproduction and Pregnancy Data

N/A

7.6.3 Pediatrics and Assessment of Effects on Growth

No assessment of effects on growth was performed.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No formal studies have been conducted to evaluate the abuse potential or withdrawal and rebound effect. The abuse potential of Venofer is likely to be low.

## 7.7 Additional Submissions / Safety Issues

None.

# 8 Postmarket Experience

The sponsor conducted a post-marketing database search for pediatric case reports. The following tables summarize the case reports by age group. A total of 86 pediatric cases were identified and a few reports were duplicated cases. The most frequently reported events were hypersensitivity reactions. Other adverse events included gastrointestinal disorders and injection site reactions.

One death was reported from Iraq in a 1 year-old boy with CKD by Vifor. The patient received 40 mg Venofer infusion over 30 minutes. The child developed “red skin” about 12 hours after Venofer infusion and was instructed by physician to be treated with diphenydramin. The patient later experienced cardiovascular collapse and died. Vifor considered this case more likely to be overdose since the recommended dose was 27 mg (3 mg/kg) for this patient. However, a delayed anaphylactic reaction cannot be excluded.

Five cases of necrotizing enterocolitis in premature neonates including 2 deaths were reported in 2000 from one hospital in a study in France (2 hospitals participated). The study was designed to compare the use of Venofer plus epoetin to oral iron plus epoetin in very low birth weight premature infants. Venofer was administered at 7 mg/kg infusion over 1 hour. Because of these case reports a PMC (#1) was issued when Venofer was initially approved in the U.S. in 2000 and labeling included these cases under Pediatric Use section. The sponsor submitted detailed information on these cases to address the PMC#1 in 2001. Since necrotizing enterocolitis is common in premature infants and no necrotizing enterocolitis was reported in study patients in the other hospital, a definite causal relationship cannot be made. However, a relatively high dose of Venofer was used in the study and no subject in the oral iron group in the same hospital reported necrotizing enterocolitis, Venofer cannot be excluded as a contributing cause for these events. The PMC submission was reviewed and the information on these cases has remained on current labeling (see review by Min Lu, M.D., 9/20/2002). No additional case has been reported since then.

**Table 22. Summary of Post-marketing Pediatric Case Reports by Age Group**

***Less than 2 years***

| Case # | Age | Gender | Key AE terms | Comments |
|---|---|---|---|---|
| 2006-01734 | 8 months | F | Bronchospasm, laryngeal edema | |
| 2009-00426 | 20 months | F | Dermatitis, pediatric off label use | |
| 2009-00888 | 1 year | M | State of shock (faint heart beats, pallor, undetectable blood pressure, feeble), redness of skin, overdose | Died |
| 2009-01156 | Neonate | F | Atrio ventricular septum defect, premature birth, bradycardia intrauterine | |
| 2010-00003 | 18 months | M | Anaphylactoid shock (low blood pressure, urticaria) | |
| 2010-00985 | 20 months | M | Skin discoloration, extravasation | |
| 2010-01434 | 1 year | F | Immediate type hypersensitivity reaction grade IV, tachycardia, diarrhea, hypotension | |
| 2010-01577 | 3 months | F | Anaphylactic reaction | |
| 2011-00955 | 2 months | M | Exposure during lactation, no adverse event | |
| 2012-00468 | 27 days | F | Necrotozing enterocolitis (grade II) | |
| 2012-00471 | 1 month | M | Necrotizing enterocolitis (stage IIIb) | Died |
| 2012-00473 | Neonate | M | Necrotizing enterocolitis (stage IIIb), severe intra-ventricular hemorrhage | Died |
| 2012-00515 | 26 days | F | Necrotizing enterocolitis (stage II bell) | |
| 2012-00516 | 1 month | F | Necrotizing enterocolitis (stage IIa Bell's classification) | |
| 2012-00604 | 21 months | M | Anaphalactoid reaction (swelling of lips, dusky color and blue lips, oxygen saturation decreased, lethargy, pallor), overdose | |

***2-5 years***

| Case # | Age | Gender | Key AE terms | Comments |
|---|---|---|---|---|
| 2006-00014 | 3 years | M | Abdominal pain, nausea, vomiting, aspartate aminotransferase increased, alanine aminotransferase increased | |
| 2006-01700 | 5 years | F | Bronchial secretion excessive, face edema, nausea, vomiting | |
| 2007-00160 | 2 years | F | Anaphylactic shock (consciousness decreased, hypotension), overdose | |
| 2009-00516 | 41 months | M | Rhabdomyolysis | |
| 2009-00909 | 3 years | Unknown | Extravasation, injection site swelling, injection site pain, bluish discoloration at injection site | |
| 2012-00429 | 4 years | M | Anaphylactoid shock (generalized edema) | |
| 2012-00599 | 2 years | M | diarrhea | |

*6-12 years*

| Case # | Age | Gender | Key AE terms | Comments |
|---|---|---|---|---|
| 2006-00179 | 7 years | M | Hypotension, facial heat, paraesthesia in hands & feet | |
| 2006-01851 | 8 years | F | Abdominal pain, nausea, vomiting, tachycardia, pallor, malaise | |
| 2007-00434 | 9 years | M | Pulmonary embolism | |
| 2010-00711 | 12 years | F | Splenomegaly, abdominal pain, drug administration rate too fast | |
| 2012-00427 | 12 years | M | Anaphylactoid reaction (hypotension, retrosternal pain, perspiration, rash, violent headache) | |
| 2012-00544 | 6 years | Unknown | Fever, headache | Duplicate of 00545 & 546 ? |
| 2012-00545 | 6 years | Unknown | Fever, headache | Duplicate of 00544 & 546 ? |
| 2012-00546 | 6 years | Unknown | Fever, headache | Duplicate of 00544 & 545 ? |
| 2012-00609 | 7 years | M | Cyanotic spell, thrombus in right ventricular | |
| 2012-01047 | 10 years | F | Infusion site hematoma, extravasation (infusion site pain), off label use | |

*13-17 years*

| Case # | Age | Gender | Key AE terms | Comments |
|---|---|---|---|---|
| 2006-00080 | 13 years | M | Abdominal pain, lips edema, nausea | |
| 2006-00301 | 17 years | F | Hypotension, dizziness, sweating increased, vomiting | |
| 2006-01197 | 17 years | F | Abdominal pain, joint soreness, swelling of both hands & some swelling of her ankles and feet | |
| 2006-01346 | 17 years | F | Anaphylactoid reaction | |
| 2006-01465 | 17 years | Unknown | Abdominal pain, flushing, nausea, hypotension | |
| 2007-00024 | 16 years | M | Anaphylactoid reaction, vomiting, nausea, fever, chills | |
| 2007-00054 | 16 years | F | Pain in the axilla, myalgia | |
| 2007-00071 | 16 years | F | Septic shock, diffuse pains, hyperthermia, infection | |
| 2007-00171 | 17 years | F | Weakness, headache, hypertension arterial, azotemia increased | |
| 2007-00266 | 13 years | F | Anaphylactoid reaction (tachycardia, fever, dyspnea, chills), condition aggravated | |
| 2007-00270 | 17 years | F | Paravenous application (injectin site inflammation, injection site discoloration, injection site pain, paraesthesia) | |
| 2007-00303 | 17 years | F | Depressed mood, shivering, abdominal pain upper, arthralgia, circulatory collapse, headache | |
| 2008-00052 | 15 years | F | Anaphylactoid reaction (body pain, anxiety, tachycardia, thready pulse, hives, edema, hypotension, dyspnea), drug administration rate too fast, off label use | |
| 2008-00125 | 17 years | F | Itching at injection site, exanthema at injection site | |
| 2008-00132 | 17 years | F | Extravasation (swelling at the infusion site) | |
| 2008-00335 | 15 years | M | Extravasation (edema at injection site) | |
| 2009-00687 | 13 years | F | Infusion site extravasation | |
| 2009-00952 | 17 years | F | Hives on lower legs, abdomen, underside of the left arm; injection site discomfort | |
| 2010-00004 | 15 years | F | Anaphylactoid reaction (tachycardia, abdominal pain, bronchospasm, laryngeal edema, malaise) | |

*13-17 years (continued)*

| Case # | Age | Gender | Key AE terms | Comments |
|---|---|---|---|---|
| 2010-00992 | 16 years | F | Anaphylactoid reaction (respiratory distress, hives on the arms & legs, swelling of the feet, arm & leg pain, shortness of breath, abdominal cramping, numbness, tingling of the arms & legs) | |
| 2011-00773 | 15 years | M | Right ear swollen lymph node, decreased appetite, coughing, tightness in throat, nasal discharge, ear pain, muffled sensation, right ear swollen lymph node, feeling of fullness, fever, headaches, vomiting, nausea associated with eating, iron levels were going down instead of up, off label use | |
| 2011-01755 | 17 years | F | Quincke's edema | |
| 2012-00319 | 17 years | F | Pain, joint ache, maximum single dose slightly increased | |
| 2012-00395 | 17 years | M | Severe headache, vomiting, general malaise, overdose | |
| 2012-00597 | 17 years | F | Dizziness, vomiting, nausea | |
| 2012-00742 | 14 years | F | Cyanosis peripheral, feeling anxious, not feeling good, cramping, off label use, rash, swelling of feet & hands, joint swelling, joint pain, shortness of breath, ankle swelling | |
| 2012-01066 | 15 years | F | Body aches, facial swelling, thready pulse, anxiety, hypotension, incorrect dose administered | |
| 2008-00043 | 16 years | F | Anaphylactoid reaction (urticaria, hypotension, tachycardia) | |

*Age uncertain*

| Case # | Age | Gender | Key AE terms | Comments |
|---|---|---|---|---|
| 2006-00036 | Child | F | Anaphylactic shock, hypotension, tachycardia | |
| 2008-00447 | Child | Unknown | Injection site extravasation, skin discoloration | Literature case |
| 2008-00448 | Child | Unknown | Injection site extravasation, skin discoloration | Literature case |
| 2008-00449 | Child | Unknown | Blood iron oversaturation | Literature case |
| 2008-00450 | Child | Unknown | Blood iron oversaturation | Literature case |
| 2008-00451 | Child | Unknown | Blood iron oversaturation | Literature case |
| 2009-00908 | Child | Unknown | Paravenous injection, lump at injection site | |
| 2011-00519 | Child | F | Extravasation, redness of infusion site, infusion site discoloration, swollen infusion site | |
| 2011-01133 | Child | M | Allergic reaction | |
| 2011-01134 | Child | M | Allergic reaction | |
| 2011-01712 | Child | F | Infiltration | |
| 2012-00304 | Child | Unknown | Allergic reaction, vomiting | Literature case |
| 2007-00223 | Adolescent | F | Pyrexia, myalgia, nausea, headache | |
| 2008-00055 | Adolescent | Unknown | Pruritis | Literature case |
| 2008-00056 | Adolescent | Unknown | Pruritis | Literature case |
| 2008-00057 | Adolescent | Unknown | Pruritis | Literature case |
| 2008-00058 | Adolescent | Unknown | Pruritis | Literature case |
| 2008-00059 | Adolescent | Unknown | Headache | Literature case |
| 2008-00060 | Adolescent | Unknown | Headache | Literature case |
| 2008-00061 | Adolescent | Unknown | Headache | Literature case |
| 2008-00062 | Adolescent | Unknown | Iron overload | Literature case |
| 2008-00063 | Adolescent | Unknown | Iron overload | Literature case |
| 2008-00064 | Adolescent | Unknown | Abdominal pain | Literature case |
| 2008-00065 | Adolescent | Unknown | Muscle cramps | Literature case |
| 2008-00066 | Adolescent | Unknown | Hypotension | Literature case |
| 2009-01164 | Adolescent | M | Dyspnea | |

**Reviewer's Comments:**

The reported safety profiles in pediatric patients with CKD were similar to those in adult patients with CKD. No specific safety issue is identified for pediatric patients with CKD based on the available data. For iron maintenance, the safety data in pediatric patients is limited to 3 month treatment duration. For chronic maintenance treatment, safety data for a minimum of one year treatment in pediatric patients with CKD should be collected.

## 9 Appendices

### 9.1 Literature Review/References

N/A

### 9.2 Labeling Recommendations

This reviewer has the following recommendations to each section for the proposed labeling:

- Indication and Usage (Section 1): Delete wording (b) (4) as follows:

  Venofer is indicated for the treatment of iron deficiency anemia in patients with chronic kidney disease

- Dosage and Administration (Section 2): Add 2.4 and 2.5 as follows:

  2.4 Pediatric Patients (2 years of age and older) with HDD-CKD for iron maintenance treatment
  Administer Venofer at a dose of 0.5 mg/kg, not to exceed 100 mg per dose, every two weeks for 12 weeks given undiluted by slow intravenous injection over 5 minutes or diluted in 25 mL of 0.9% NaCl and administered over 5 to 60 minutes.

  The dosing for iron replacement treatment in pediatric patients with HDD-CKD has not been established.

  2.5 Pediatric Patients (2 years of age and older) with NDD-CKD or PDD-CKD who are on erythropoietin therapy for iron maintenance treatment
  Administer Venofer at a dose of 0.5 mg/kg, not to exceed 100 mg per dose, every four weeks for 12 weeks given undiluted by slow intravenous injection over 5 minutes or diluted in 25 mL of 0.9% NaCl and administered over 5 to 60 minutes.

  The dosing for iron replacement treatment in pediatric patients with HDD-CKD has not been established.

- Adverse Reactions (Section 6): Add subsection for pediatric patients as follows:

> **Adverse Reactions in Pediatric Patients with CKD (ages 2 years and older)**
> In a randomized, open-label, dose-ranging trial for iron maintenance of Venofer in pediatric patients with CKD on stable erythropoietin therapy [see Clinical Studies (14.6)], at least one treatment-emergent adverse reaction was experienced by 57.4% (27/47) of the patients receiving Venofer 0.5 mg/kg, 53.2% (25/47) of the patients receiving Venofer 1.0 mg/kg, and 55.3% (26/47) of the patients receiving Venofer 2.0 mg/kg. A total of 5 (10.6%) patients in the Venofer 0.5 mg/kg group, 10 (21.3%) patients in the Venofer 1.0 mg/kg group, and 10 (21.3%) patients in the Venofer 2.0 mg/kg group experienced at least 1 serious adverse reaction during the study. The most common treatment-emergent adverse reactions (> 2% of patients) in all patients were headache (5.7%), respiratory tract viral infection (4.3%), peritonitis (3.5%), vomiting (3.5%), pyrexia (3.5%), dizziness (3.5%), cough (3.5%), renal transplant (3.5%), nausea (2.8%), arteriovenous fistula thrombosis (2.1%), hypotension (2.1%), and hypertension (2.1%).

- Use in Special Population (Section 8): Add the following under 8.4.

> **8.4 Pediatric Use**
> Safety and effectiveness of Venofer for iron maintenance treatment in pediatric patients with CKD have been studied in a trial in patients at age 2 years and older with HDD-CKD, PDD-CKD, or NDD-CKD. Venofer at doses of 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg was administered in pediatric patients with CKD. All three doses maintained hemoglobin between 10.5 g/dL and 14.0 g/dL in about 50% of subjects over the 12-week treatment period with stable EPO dosing [See Clinical Studies (14.6)]
>
> Venofer has not been studied in patients younger than 2 years of age.

- Clinical Studies (Section 14): Add pediatric study and results as follows:

> **14.6 Study F: Maintenance Dosing in Pediatric Patients Ages 2 years and Older with Chronic Kidney Disease**
> Study F was a randomized, open-label, dose-ranging study for iron maintenance treatment in pediatric patients with CKD on stable erythropoietin therapy. The study randomized patients to one of three doses of Venofer (0.5 mg/kg, 1.0 mg/kg or 2.0 mg/kg). The mean age was 13 years ranging from 2 to 20 years. Over 70% of patients were 12 years or older in all 3 groups. There were 84 males and 61 females. About 60% of patients underwent hemodialysis and 25% underwent peritoneal dialysis in all three dose groups. At baseline, the mean hemoglobin was 12 g/dL, the mean TSAT was 33% and the mean ferritin was 300 ng/mL. Patients with HDD-CKD received Venofer once every other week for 6 doses. Patients with PDD-CKD or NDD-CKD received Venofer once every 4 weeks for 3 doses. Among 131 evaluable patients, the proportions who maintained hemoglobin between 10.5 g/dL and 14.0 g/dL during the 12-week treatment period with a stable erythropoietin dosing were 58.7%, 46.7%, and 45.0% in the Venofer 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg groups, respectively. A dose-response relationship was not demonstrated.

### 9.3 Advisory Committee Meeting

No AC meeting is planned.

---

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

---

/s/

---

MIN LU
08/31/2012

KATHY M ROBIE SUH
08/31/2012