

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-135

MEDICAL REVIEW(S)

DIVISION OF GASTROINTESTINAL AND COAGULATION
DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA: 21-135 (BM, BS, SU, BZ, AM, C)

Sponsor: Luitpold Pharmaceuticals, Inc.

Drug name: Venofer (Iron Sucrose Injection)

Date submitted: August 6, 1999; October 15, 1999;
October 22, 1999; October 27, 1999;
November 16, 1999; November 22, 1999;
December 7, 1999; December 15, 1999;
January 14, 2000; February 2, 2000;
February 22, 2000; April 19, 2000;
May 5, 2000; May 15, 2000; May 31, 2000;
June 6, 2000; June 13, 2000; June 16, 2000;
June 30, 2000; August 10, 2000

Date assigned: September 20, 1999

Review completed: October 13, 2000

Medical Reviewer: Min Lu, M.D., M.P.H.

APPEARS THIS WAY
ON ORIGINAL

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Acronyms and Abbreviations

ACE	Angiotensin-converting enzyme
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BUN	Blood urea nitrogen
Ca	Calcium
CDAI	Crohn's disease activity index
CI	Confidence interval
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	Case report form
CVA	Cerebrovascular accident
dl	Deciliter
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EPO	Erythropoietin
ESRD	End stage renal disease
Fe (III)	Iron(III)
fl	Femtoliter (10 ⁻¹⁵ liter)
g	Gram
GGT	Gamma-glutamyl transferase
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
Hct	Hematocrit
HIV	Human immunodeficiency virus
ITT	Intent-to-treat
IV	Intravenous
LDH	Lactic dehydrogenase
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
mg	Milligram
ml	Milliliter
NaCl	Sodium chloride
NFK-DOQI	National Kidney Foundation-Dialysis Outcomes Quality Initiative
ng	Nanogram
QD	Once a day
pg	Picogram
PP	Per-protocol
PSUR	Periodic safety update report
PTH	Parathyroid hormone
r-HuEPO	Recombinant human erythropoietin
RBC	Red blood cell
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SEM	Standard error of the mean
SLE	Systemic lupus erythematosus
TIBC	Total iron binding capacity
TSAT	Transferrin saturation
WBC	White blood cell
WHO	World Health Organization
yrs	Years

SUMMARY

1. Recommendations:

- 1). **Venofer should be approved for "treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy" with labeling recommendations as provided in attached Appendix 5.**

A Phase IV study should be conducted to obtain more information on anaphylactic/anaphylactoid reactions for Venofer treatment in hemodialysis patients. The sponsor should provide information about the use of Venofer in the pediatric population.

The major clinical deficiencies are:

- (1) No adequate and well-controlled study is provided to support the desired claim.
- (2) Study 50 (Gasche) was a pilot study to evaluate the efficacy of erythropoietin treatment in addition to Venofer therapy in patients with Crohn's disease associated anemia but not to evaluate the efficacy of Venofer treatment. This study did not provide evidence of stable baseline hemoglobin and stable Crohn's disease condition to support the baseline and end of treatment comparison.
- (3) Study 52 (Bulvik) was a nonrandomized study and no study protocol was available. The study did not demonstrate superiority of Venofer over Ferrlecit (not approved indication) in treatment of iron deficiency anemia in these patients and was not specifically designed as an equivalence or non-inferiority trial. The Venofer group had significantly higher hemoglobin and hematocrit than the Ferrlecit group at baseline that may bias the result in favor of Venofer. The study did not provide stable baseline hemoglobin to support baseline and end of treatment comparison. Many patients (36.3%) did not complete the study.

To obtain the desired indication, the sponsor should conduct an adequate and well-controlled study providing a strong result to demonstrate efficacy of Venofer in patients

No adequate and well-controlled study is provided to support the requested claim. To obtain the desired claim, the sponsor should conduct an adequate and well-controlled study providing a strong result to demonstrate efficacy of Venofer in patients

The major deficiencies are:

- (1) Studies LU98002 (23 patients with anaphylactoid reactions) and LU98001 (10 patients with anaphylactoid reactions) did not provide detailed clinical information on symptoms, time of event, intervention and outcome of anaphylactoid reactions to iron dextran at baseline in study patients to validate these reactions.
- (2) About 48% of patients enrolled in the study LU98002 did not satisfy the inclusion criteria according to the definition of anaphylactoid reaction to iron dextran defined in the study protocol.
- (3) Monitoring for anaphylactoid reaction within the first hour of drug administration was not described in LU98001 protocol.
- (4) Some patients in LU98002 and LU98001 who had intolerance or anaphylactoid reaction to iron dextran also had intolerance or anaphylactoid reaction to Venofer.

To obtain the desired claim, the sponsor should conduct an adequate and well-controlled study (including adequate size, validation of prior reaction to iron dextran, clearly defined study endpoint)

2. Summary of Clinical Findings:

The sponsor has submitted an NDA to support Venofer injection as an intravenous iron preparation for the following four indications:

- 1) Dialysis-associated iron deficiency anemia.

Three pivotal trials (LU98001, LU98002 and VIFOR/001) and 4 supportive studies (Al-Momen, Yavuz, Hussain and Schaefer) were submitted to support the indication for iron deficiency anemia in hemodialysis patients:

LU98001 was a multicenter, open-label, historically-controlled study in 101 hemodialysis patients (77 patients in the Venofer group and 24 patients with matched ferritin level in the historical control group). LU98001 demonstrated a significant increase in hemoglobin level after Venofer treatment compared to the historical control population at end of treatment ($p=0.0085$), 2 week follow-up ($p=0.0001$) and 5 week follow-up ($p=0.041$). LU98002 (23 patients) and VIFO/001(132 patients) were multicenter, baseline-controlled studies which also showed a significant increase in hemoglobin level after Venofer treatment ($p=0.0003$)

and $p < 0.0001$, respectively) and were consistent with the study result in LU98001. The treatment effect of Venofer was 1 g/dl increase in hemoglobin after 1 g iron given as Venofer injection in 10 dialysis sessions over 4 weeks from two pivotal trials (LU98001 and LU98002). The study results in the pivotal trials were supported by three supportive studies where a statistically significantly higher hemoglobin level was observed in patients who received IV iron sucrose than those who did not receive iron sucrose [Al-Momen ($p < 0.001$), Yavuz ($p < 0.05$) and Hussain ($p < 0.01$)]. One supportive study (Schaefer) did not show a significant increase in hemoglobin after Venofer treatment ($p > 0.05$) or after treatment with active comparator (Ferrlecit). This reviewer recommends that Venofer injection be approved for treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy.

Study 50 (Gasche) was a pilot study to evaluate the efficacy of erythropoietin treatment in addition to Venofer therapy in 40 patients with Crohn's disease associated anemia but not to evaluate the efficacy of Venofer treatment. The mean increase in hemoglobin from baseline in patients who received only Venofer treatment (200 mg 18 doses) was 3.3 g/dl. However, this study did not provide evidence of stable baseline hemoglobin and stable Crohn's disease condition to support baseline and end of treatment comparison. Study 52 (Bulvik) was a nonrandomized, open-label, parallel group study of Venofer versus Ferrlecit in 123 patients with iron deficiency anemia who had malabsorption and intolerance to oral iron. No study protocol was available. Study 52 did not demonstrate superiority of Venofer over Ferrlecit in treatment of iron deficiency anemia ($p > 0.05$) in these patients and the study was not specifically designed as an equivalence or non-inferiority trial. The Venofer group had significantly higher hemoglobin and hematocrit than the Ferrlecit group at baseline that may bias the result in favor of Venofer. The study showed a significant increase in mean hemoglobin from baseline in the Venofer group ($p < 0.001$). Again, the study did not provide stable baseline hemoglobin to support baseline and end of treatment comparison.

Study 52 (Bulvik) was a nonrandomized, open-label, parallel group study of Venofer versus Ferrlecit in 123 patients with iron deficiency anemia who had malabsorption and intolerance to oral iron. As mentioned above, the study was not an adequate and well-controlled study.

Study LU98002 enrolled 23 hemodialysis patients and Study LU98001 enrolled 10 hemodialysis patients with anaphylactoid reactions to iron dextran. Neither study provided detailed clinical information on symptoms, time of event, intervention and outcome of anaphylactoid reactions to iron dextran at baseline for study patients to validate these reactions. In Study LU98002, only 12 patients (52%) of 23 enrolled patients satisfied the inclusion criteria according to the definition of anaphylactoid reaction to iron dextran defined in the study protocol. In addition, two patients enrolled in the study experienced anaphylactoid reaction to Venofer treatment. This suggests that patients who have intolerance or anaphylactoid reaction to iron dextran may also have intolerance or anaphylactoid reaction to Venofer. In Study LU98001, monitoring for anaphylactoid reaction within the first hour of drug administration was not described in the study protocol. One (10%) of ten patients who had a history of anaphylactoid reaction to iron dextran according to the sponsor also reported anaphylactoid reaction to Venofer treatment.

Venofer has been used as an iron sucrose intravenous preparation for 50 years in Switzerland and has been marketed in 35 countries world-wide. A total of 4099 patients (2416 end-stage renal disease patients and 1683 other patients) have been exposed to at least one dose of iron sucrose in 74 study reports/publications. Venofer was clearly identified as study drug in 32 reports/publications. Overall, about 30% of these patients were exposed to 100 mg dosage, 30% to 200 mg dosage, and 5% to 500 mg or greater dosage. In three pivotal trials in hemodialysis patients, 231 (99.6%) patients received at least one dose of Venofer. All patients received Venofer 100 mg in each dialysis session during the treatment. Among 231 patients, 70 (91%) patients in LU98001 and 20 (87%) patients in LU98002 received a total of 10 Venofer treatment doses (1 g of elemental iron), and 111 (85%) patients in VIFOR/001 received the total Venofer treatment dose as scheduled according to baseline hemoglobin and weight.

Thirteen reports/publications including 1111 end-stage renal disease patients and 18 reports/publications including 1151 other patients reported at least one adverse event in their study results. In three pivotal trials, 80% of 231 hemodialysis patients reported at least one adverse event during or following the Venofer treatment period. The common adverse events of Venofer treatment were hypotension (39%), cramps (27%), nausea (17%),

headache (12%), vomiting (9%), chest pain (7%), dizziness (7%), diarrhea (6%), abdominal pain (5%), and hypertension (5%). Three patients died in three pivotal trials. The causes of these deaths were hypoglycemia reaction or myocardial infarction, coumadin necrosis, and rejection of renal transplant. All deaths were considered not related to study drug by investigators. A total of 42 patients (18%) experienced serious adverse events during the study in three pivotal trials. The most common serious adverse events were pneumonia (3%), vascular access problem (2%), GI bleeding (1%), cellulitis (1%), pleural effusion (1%), hypoglycemia (1%), chest pain (1%), angina pectoris (1%), sepsis (1%), graft rejection (1%), and accidental injury (1%). A total of 9 patients (4%) discontinued Venofer treatment permanently and 5 patients (2%) discontinued temporarily due to adverse events in three trials.

No life-threatening or serious anaphylactic/anaphylactoid reactions were reported in three pivotal trials. Five patients developed pruritus, urticaria, or rashes after Venofer treatment and were considered as having anaphylactoid reactions. The incidence of anaphylactoid reactions was 3% in patients (LU98001 and LU98002) where the test dose was not given, and 1.5% in patients (VIFOR/001) where a negative test dose was required in study enrollment. Dyspnea and hypotension were not included in the above figure because of lack of sufficient clinical information to determine if those symptoms were due to underlying disease or anaphylactoid reaction. Overall, no patient discontinued treatment due to these reactions. Anaphylactoid reactions have been reported in 2.9% of 455 hemodialysis patients in 8 published studies [urticaria/skin discomfort (1.8%), wheezing (0.4%), hypotension (0.7%)].

There were much lower incidences of anaphylactic/anaphylactoid reactions reported by post-marketing pharmacovigilance data from 11 countries between 1992-1997 (0.017%) and in the post-marketing safety report from Vifor (Venofer manufacturer) between October 1997 and August 1999 (0.0055%) using a spontaneous reporting system. A total of 27 cases of anaphylactic/anaphylactoid reactions were reported by Vifor during that period. Eight of these (0.0016%; 6 reported between March 1999 and August 1999) were serious anaphylactic/anaphylactoid reactions (anaphylactic shock, loss of consciousness, collapse, dyspnea, hypotension, or convulsion) which were considered related to Venofer treatment. There were two fatal cases (cardiac arrest) which occurred in September 1999 following Venofer infusion reported from India; one of these patients had chronic renal failure and anemia. No detailed information is provided for these cases. Two deaths and 3 serious cases of necrotizing enterocolitis in pre-term infants in a French study were reported in April 2000. No detailed information about these cases is available at the time of this review.

This reviewer recommends that a warning statement for life-threatening anaphylactic/anaphylactoid reaction be included in the labeling. A Phase IV study with appropriate size to obtain further information regarding anaphylactic/anaphylactoid reactions should be conducted. A recommendation for serum ferritin level monitoring during the treatment should be stated clearly in the labeling.

The sponsor should provide information on the use of Venofer in the pediatric population.

1. Background and Rationale

1.1 Background

The primary cause of anemia in patients with chronic renal failure is insufficient production of erythropoietin (EPO) by the diseased kidney. Additional factors that may cause or contribute to the anemia include iron deficiency. Iron deficiency in hemodialysis patients may be due to several reasons including substantial losses of blood from frequent blood tests, blood remaining in the dialysis tubing and dialyzer, gastrointestinal blood losses, and increases in the rate of erythropoiesis on epoetin (i.e., Epoetin alfa, recombinant human erythropoietin [r-HuEPO]) therapy. When untreated, the anemia of chronic renal failure is associated with decreased tissue oxygen delivery, increased risk of left ventricular hypertrophy, decreased cognition and mental acuity and impaired immune responsiveness, which reduce quality of life and patient survival.

Oral iron supplementation is often inadequate to maintain iron stores in most epoetin-treated hemodialysis patients due to inadequate absorption, poor compliance, and side effects including gastric irritation and constipation. Intravenous iron may improve responsiveness to epoetin in hemodialysis patients and may reduce the amount of epoetin needed to achieve and maintain a target hematocrit (Hct)/hemoglobin (Hb) in hemodialysis patients.

The National Kidney Foundation Dialysis Outcome Quality Initiative Clinical Practice Guideline for Treatment of Anemia of Chronic Renal Failure (1997) recommends the target hematocrit (hemoglobin) should be 33% (11g/dl) for EPO therapy; sufficient iron should be administered to maintain a TSAT of $\geq 20\%$, and a serum ferritin level of ≥ 100 ng/mL so that chronic renal failure patients can achieve and maintain a target hematocrit/hemoglobin in conjunction with EPO use. The guideline indicated that most hemodialysis patients would require intravenous iron on a regular basis to achieve and maintain a target hematocrit/hemoglobin.

In the United States, iron dextran and iron gluconate are currently intravenous iron preparations used in hemodialysis patients.

Intravenous iron may also be used in other patient population with documented iron deficiency in whom oral administration is unsatisfactory or impossible. In United States, iron dextran is currently used in this setting.

1.2 Indication

The sponsor has submitted this NDA to support Venofer use for the following 4 indications:

- Dialysis-associated iron deficiency anemia
-
-
-

1.3 Rationale

In the United States, the intravenous iron preparation iron dextran has been used in hemodialysis patients and iron gluconate (Ferrelecit) has been recently approved (February 18, 1999) for the treatment of iron deficiency anemia in chronic renal dialysis patients on supplemental erythropoietin therapy.

The major problem associated with use of iron dextran is occurrence of life-threatening anaphylactic-like reaction which has a reported incidence of 0.65% (3 of 471 general patients) and 0.7% (4 of 573 dialysis patients). Iron gluconate also has been associated with anaphylactic-like reaction but with a relatively low incidence rate.

Venofer (iron sucrose) consists of polynuclear ferric hydroxide cores surrounded by noncovalently-bound sucrose molecules. Iron sucrose differs from iron dextran in its molecular weight and may elicit a lower incidence of anaphylactoid reactions compared to iron dextran. Venofer has a suitable complex stability, which allows a competitive exchange of iron between iron sucrose and selective iron-binding proteins such as transferrin and ferritin. The pharmacokinetic studies suggest that the administered iron disappears very rapidly from the serum, thus Venofer may provide a rapid correction of iron deficiency anemia.

1.4 Foreign marketing

Venofer was first approved as a prescription medicine in February 1950 in Switzerland. The sponsor provided the world-wide market authorization status reported by the manufacturer Vifor (international), Inc (See Appendix 1). From 1950 to August 1999 Venofer has received regulatory approval for marketing authorization in 35 countries. Three countries (Italy, Taiwan and Greece) had voluntary marketing application withdrawal by the company. The reasons for withdrawal were not provided

Venofer is currently distributed on a "Named Patient" basis ("compassionate use") in 16 countries including Australia, Austria, Belgium, Canada, Denmark, Egypt, Finland, Greece, Hungary, Iceland, Iran, Ireland, Norway, Pakistan, South Africa and Sweden.

2. Material Reviewed

The following material in the NDA submission was reviewed:

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Summary table of material reviewed

Volumes	Contents	Submission Date	Receipt Date
1.1	Introductory summary	08/06/1999	08/06/1999
1.3	Summary: chemistry, pharmacology and toxicology, human pharmacokinetics and bioavailability		
1.4	clinical data summary and results of statistical analysis		
1.18	Clinical trials in chronic renal failure patients		
1.18-1.27	Study VIFOR/001		
1.28-1.29	Study LU98001		
1.30	Study Al-Momen and Study Yavuz		
1.31-1.33	Study Hussian and Study Schaefer		
1.34-1.35	Other study reports in patients with chronic renal failure		
1.36	Studies in other population		
1.37	Study 50		
1.38	study 52		
1.40	Integrated summary of efficacy and safety		
1.41-1.42	Reports and publication		
1.43	Drug abuse and overdose potential, integrated summary of benefits and risks of venofer		
Amendment 002	Certified translation of the Anatkov article	10/15/1999	10/15/1999
A11.1	Datasets for Study LU98002 and VIFOR-001	10/27/2000	10/27/2000
11.1-11.4	Analysis of safety and efficacy by gender, race, age, and center	11/16/1999	11/16/1999
12.1-12.2	Analysis of safety and efficacy by gender, race, age, and center	11/22/1999	11/22/1999
13.1-13.2	Withdrawals in Study Al-Momen and Study 52	12/07/1999	12/07/1999
14.1-14.11	Safety update and Study LU98001		
BM	Responses to questions in integrated safety summary	01/14/2000	01/15/2000
15.1	Study 51 withdrawal for inspection	02/02/2000	02/03/2000
A16.1	Dataset for Study LU98001	02/22/2000	02/22/2000
17.1 BM	Issues in studies performed by Dr. Stephen Zeig	04/19/2000	04/20/2000
C	Datasets	05/15/2000	05/16/2000
17.1 BZ	Datasets for LU98002 and VIFOR/001	05/31/2000	05/31/2000
17.1 BS	Issues in VIFOR/001 Dataset	06/13/2000	06/14/2000
17.1 BM	Historical control protocol	06/16/2000	06/16/2000
20.1-20.4 AM	Historical control data	06/30/2000	06/30/2000
C	Additional analysis	08/10/2000	08/10/2000

Reviewer's table

Material in IND Volume 7.1-8.1 submitted between October 1999 to July 2000 was reviewed for safety.

3. Chemistry

Venofer is a brown, aqueous solution containing an alkaline iron(III)-hydroxide sucrose complex and water for injection. The iron(III)-hydroxide sucrose complex has a molecular weight of approximately 43,200 dalton and a structural formula as follows:



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

Other chemical names synonymous with the drug substance are Ferric-hydroxide Sucrose Complex and Saccharated Iron Oxide.

Venofer is supplied as 5 ml single dose vial. Each 5 ml contains 100 mg of elemental iron as iron sucrose in water for injection.

4. Pharmacology and Toxicology Information

The following are findings from animal studies in the sponsor's report:

- The lowest LD₅₀, 140 mg Fe/kg, was observed in male rats following a single IV injection of iron sucrose; the maximum non-lethal dose was 75 mg iron/kg;
- Intravenously administered iron sucrose possesses the desired properties of rapid distribution from the plasma and uptake into the tissues where it is available for erythropoiesis;
- Storage in tissues is mainly associated with the reticuloendothelial system, thus leading to a low potential for toxicity. Adverse effects in the toxicity studies are attributable to excessive iron intake and no target organ toxicity has been observed.

5. Human Pharmacology and Pharmacokinetics

5.1 Summary table of studies

The following table summarizes the bioavailability, pharmacokinetics and pharmacodynamics studies:

BIOPHARMACEUTICS STUDY SUMMARY

Study: Principal Investigator (Author), Year[Ref]	Study Design	Route/Vol/Rate ^a	Iron Dose (mg)	No. of Subjects Treated with Iron Sucrose	Batch No./ Plant/Date of Manufacture ^b	Study Report (Yes/No)	Publication (Yes/No)
Pharmacokinetics and Bioavailability Studies for Iron Sucrose							
MacDougall, 1999 [1]	Single-center, randomized, open, parallel, single dose study comparing iron sucrose, iron dextran and iron dextrin for effect on hematological and serum iron parameters in patients with anemia of chronic renal failure	IV/100 mL/30min	200	20	535109 A1, 692109 A1, 554209 A2/ [redacted]	Yes	Yes
Major, 1997 [2]	Controlled, randomized, parallel group, single dose study comparing the effect of EPO with and without iron sucrose on reticulocytes in healthy subjects	IV/NR/NR	200	7	[redacted]	Yes	Yes
Danielson, 1996 [3]	Open, single dose pharmacokinetic study in healthy subjects	IV/15 mL/5min	100	12	445209B1/ [redacted]	Yes	Yes
Krysko, 1984 [4]	Open, cross-over, single dose pharmacokinetic study in healthy subjects with ⁵⁹ Fe-labeled iron sucrose	IV/NR/NR	50	11	[redacted]	No	Yes
Beshara, 1997 [5]	Open, single dose study for determination of utilization and incorporation of iron in red blood cells in patients with three types of anemia using ⁵⁹ Fe/ ⁵⁵ Fe-labeled iron sucrose	IV/NR/5 min	100	6	671109/ [redacted]	Yes	No
Anatkov, 1970 [6]	Open, uncontrolled, study of the effect of high doses of iron sucrose on hematological parameters and urinary elimination in anemic patients	IV/NR/3-4 hr IV/500 mL/ 3-4 hr	700-800 500	5 21	[redacted]	No	Yes
^a : Rate of infusion of each dose of iron sucrose. ^b : Available for Venofer (Iron Sucrose), Iron Dextran and Iron Dextrin only. Vol: volume infused; NR: not reported; EPO: erythropoietin; IV: intravenously; r: milliliters; min: minutes; hr: hours							

Sponsor's table in NDA Vol. 1.3, pp. 92

BIOPHARMACEUTICS STUDY SUMMARY (continued)

Study: Principal Investigator (Author), Year [Ref]	Study Design	Route/Vol/Rate ^a	Iron Dose (mg)	No. of Subjects Treated with Iron Sucrose	Batch No./ Plant/Date of Manufacture ^b	Study Report (Yes/No)	Publication (Yes/No)
Other In Vivo Studies with Iron Sucrose							
Chandler, VIF95002, 1998 [7]	Dose range finding study with regard to tolerability in anemic patients	IV/250 mL/2 hr	200 300 400 500	89 189 35 22	572109, 670109 675109	Yes	No
Danielson, 1993 [8,9]	Open, study on effect of iron sucrose on serum iron parameters for 81 weeks, including a comparison with oral ferrous sulfate	IV/5-20mL/ 2-5 min	100	20	-	Yes	No
Al-Momen, 1994 [10]	Open, low dose and high dose iron sucrose comparative study on hematological and serum iron parameters and EPO use in hemodialysis patients	IV/250 mL/ 1-4 hr IV/25 mL/ 5-10 min	500 100	58 51	-	No	Yes
Silverberg, 1996 [11]	Open study of effect of monthly doses of iron sucrose on anemia in patients with chronic renal failure	IV/150 mL/2 hr	200	33	-	No	Yes
Van Iperen, Geisser Undated communications [12, 13]	In vitro study of binding of iron sucrose to human transferrin	Not applicable	Not applicable	Not applicable	-	No	No

a: Rate of infusion of each dose of iron sucrose.
b: Available for Vifor (International), Inc. sponsored studies only.
Vol: volume infused; NR: not reported; EPO: erythropoietin; IV: intravenously; mL: milliliters; min: minutes; hr: hours

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5.2 Summary of pharmacokinetic parameters

The sponsor indicated that the pharmacokinetics of intravenously administered iron sucrose show that maximum iron levels, averaging 538 µmol/L, occur 10 minutes after an injection of 100 mg iron. The volume of distribution at steady state is 7.3 liters, which suggests a low iron distribution in body fluids. The administered iron is quickly cleared from the serum with a half-life of 5.3 hours. The following is the sponsor's table comparing pharmacokinetic data from the key published pharmacokinetic studies.

Summary of Key Pharmacokinetic Data for Venofer®

	Anatkov & Gekova [6]	Krzysko et al [4]	Danielson et al [3]
Dose	500; 700-800 mg	50 mg	100 mg
Maximum Iron Levels:			
50 mg iron dose	-	NR	-
100 mg iron dose	-	-	537.7 ± 106.9 µmol/L (30 mg/L) at 10 min
500 mg iron dose	1398 ± 605 µg/dL (13.98 mg/L) at 4 h ^a	-	-
Mean Initial Plasma Concentration (C ₀)	NR	3.650 ± 0.775 µg/mL	631.2 ± 146.9 µmol/L
Mean Volume of Distribution (V _d)	NR	0.395 ± 0.117 L/kg	7.3 ± 2.1L
Mean Area Under The Curve (AUC)	NR	24.324 ± 15.644 µg/h/mL	1491 ± 212 µmol/L/h
Mean Urinary Excretion:			
100 mg iron dose	4-6%/24 h	NR	5%/24 h
500 mg iron dose	22.4 mg/24 h	-	5.19 ± 1.28 mg/24 h
700 mg iron dose	33.7 mg/24 h	-	-
Half Life (terminal)	NR	9.31 ± 6.77 h	5.3 ± 1.6 h
Total Body Clearance	NR	0.074 ± 0.086 L/h/kg	1.23 ± 0.22 L/h (20.5 ± 3.7 mL/min)
Iron Transported by Saturated Transferrin	NR	NR	31.0 ± 6.6 mg/24 h

NR: Not reported; h: hours(s); min: minute; kg: kilogram; µg: microgram; mL: milliliter; µmol/L: micromolar; L: liter; mg: milligram; L: liter; h: hour; dL: deciliter.
a: Following a dose of 360 mg iron as iron sucrose.

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Due to the lower stability of iron sucrose in comparison to the physiologically occurring transferrin, a competitive exchange of iron with transferrin was observed. The amount of iron transported by transferrin was 31 mg iron/24h after a single injection of iron sucrose (100 mg iron). Renal elimination of iron is low, occurring in the first 4h after injection and corresponds to less than 5% of the total body clearance (approximately 20 ml/min); after 24h the serum concentrations of iron are reduced to the pre-dose levels. Approximately 75% of the dosage of sucrose is excreted in the urine.

No classical dose-ranging studies with clinical efficacy endpoints were performed to support the doses used in the clinical trials.

6. Summary of Clinical Studies

6.1 Summary table of clinical studies

The sponsor submitted the following clinical study reports/publications in this NDA submission:

Summary of submitted clinical studies

Type of information		Number of studies, sites (year) in hemodialysis populations	Number of studies, sites (year) in other populations
Study reports	with data listing	7: 2 United States (1999), 1 South Africa (1994-1995), 1 Saudi Arabia (1994-1996) 1 Turkey (1997) 1 Pakistan (1996) 1 Germany (1997-1998)	2: 1 Austria (1993-1995) 1 Israel (1993-1998)
	without data listing or database	4	5
Publications	Full articles	10	24
	Abstracts	13	2

Reviewer's table

Summary of submitted study reports with data listing available for review

Studies (Sites)	Number of Patients	Study Design
Studies in hemodialysis populations		
Study LU98001 (United State)	101	Historically-controlled
Study LU98002 (United State)	23	Baseline-controlled
Study VIFOR/001 (South Africa)	132	Baseline-controlled
Study Al-Momen (Saudi Arabia)	123	Nonrandomized, no-treatment concurrent controlled
Study Yavuz (Turkey)	30	Nonrandomized, no-treatment concurrent controlled
Study Hussain (Pakistan)	20	Nonrandomized, treatment concurrent controlled
Study Schaefer (Germany)	59	Nonrandomized, treatment concurrent controlled
Studies in other populations		
Study 50 (Austria)	40	Baseline-controlled (for Venofer treatment)
Study 52 (Israel)	121	Nonrandomized, treatment concurrent controlled

Reviewer's table

6.2 Identification of pivotal trials

Study LU98001, LU98002 and VIFOR/001 are considered as pivotal studies for hemodialysis population. Four other studies listed above in hemodialysis population are

considered as supportive studies. Two studies in other populations will be reviewed as pivotal studies for general iron deficiency anemia.

7. Clinical Studies in Hemodialysis Patients

7.1 Pivotal clinical efficacy trials

7.1.1 Trial 1: Study LU98001 (Vol. 14.2-14.11)

Study Investigators and Study Centers:

K.R. Boren, MD, Boren Research Institute, Mesa, AZ
C. Charytan, MD, Nephrology Associates, Flushing, NY
M. Cohen DO, FACP, San Diego Dialysis Services, San Diego, CA
M. Kaptan, MD, Nephrology Associates, Nashville, TN
W. Klein, MD, Pennsylvania Dialysis Clinic of Reading, Wyomissing, PA
N. W. Levin, MD, Yorkville Dialysis Unit, New York, NY
J. Roman, MD, Dallas Nephrology Associates, Dallas, TX
S. Swann, MD, Total Renal Care. Total Renal Research, Minneapolis, MN
S. Zeig, MD, Clinical Studies, Fort Lauderdale Inpatient, Fort Lauderdale, FL

Study Period: 14 December 1998 - 27 July 1999

7.1.1.1 Study Protocol

Title of the Study: A Phase II/III Open Label Study of the Safety and Efficacy of Venofer [Iron Sucrose Injection] in Patients with Dialysis-Associated Anemia

7.1.1.1.1 Study Objective

The objective of this study was to determine the safety and efficacy of Venofer (iron sucrose injection) in iron deficient patients with dialysis-associated anemia.

7.1.1.1.2 Study Design

This study was a multicenter, open-label, historically-controlled study in patients with dialysis associated anemia.

The prospective study LU98001 was conducted in 10 sites in 77 hemodialysis patients. The duration of study participation for each patient was approximately 10 weeks including 2 weeks of screening and baseline data collection followed by 3-4 weeks of drug treatment and two follow-up evaluations. Following screening and a one week observation period, consenting qualified patients were given Venofer 100 mg at each dialysis session either as slow injection or a saline diluted slow infusion. Up to 1000mg iron was to be administered over 10 consecutive dialysis sessions. Patients were assessed for hemoglobin, hematocrit and iron indices at baseline, at the end of treatment and at two follow-up visits.

The historical control was a natural history of iron deficiency anemia study in 60 hemodialysis patients at a single site at Gambro Health Care Patient Services, Inc., in Tucson, Arizona. This study initiated in April 1998 and was close to completing up to 1

year of follow-up at the time of submission. This historical control study will be discussed later.

7.1.1.1.3 Study Population

Inclusion criteria were:

- Male or female patients over the age of 18
- Able to give informed consent
- Undergoing chronic hemodialysis three times weekly
- Receiving recombinant human erythropoietin (rHuEPO) for at least four months
- Having rHuEPO dose unchanged for two weeks
- Hemoglobin concentration greater than 8.0 and less than 11.0 g/dl for at least two consecutive weeks
- Transferrin saturation < 20%
- Serum ferritin < 300 ng/ml
- Normal serum B₁₂ and folate levels
- No other causes of anemia (SLE, rheumatoid arthritis, myeloma, etc.)
- Absence of infection, malignancy or surgery in the prior month
- Off all iron supplementation for at least 2 weeks
- No blood transfusions in the past three months

Exclusion criteria were:

- Life expectancy less than 6 months
- Elective surgery or likely transplantation within the next 6 months
- Severe diseases of the liver [decompensated] or cardiovascular system, severe psychiatric disorders, other disease which in the opinion of the investigator makes participation unacceptable
- Serum ferritin ≥ 300 ng/ml
- Serious bacterial or viral infection or acute illness [e.g. hepatitis] unless completely resolved at least 4 weeks before inclusion
- Gastrointestinal bleeding
- HIV positive or Hepatitis B positive
- Asthma
- Active inflammatory disease such as SLE or rheumatoid arthritis
- Likely need for blood transfusion during the study
- Anticipated surgery of any kind during the study
- Pregnancy or breastfeeding
- Use of any iron preparations within two weeks before blood sampling for baseline evaluation
- Participation in any other therapeutic trial within the previous month.

7.1.1.1.4 Study Drug

Venofer was supplied by Luitpold Pharmaceuticals, Inc. as 5 ml ampoules or vials, containing 100 mg iron as Fe[III] hydroxide sucrose complex and was administered through the dialysis line within 30 minutes from the start of the dialysis given over 5 minutes by injection or infusion pump. One ampoule or vial of Venofer was to be administered on each dialysis session for total 10 dialysis sessions. The total cumulative dose of Venofer to be given during the treatment period was 1000 mg. A maximum of 3 ampoules of Venofer was administered per week. Venofer therapy started on the first day of dialysis following screening and the baseline observation period [Study Day 1]. If adverse events such as hypotension (fall in SBP >30 mm Hg) occurred, subsequent doses

of Venofer may be diluted in 100 ml 0.9% NaCl, and administered by infusion over 15-30 minutes. End of treatment evaluation occurred immediately prior to the 11th dialysis session (Study Day 24).

The rHuEPO dose was to be held constant throughout the study.

No additional iron preparations were allowed until after the Day 57 evaluation.

7.1.1.1.5 Study Plan

Each patient qualifying for study inclusion according to medical history and data recorded in the medical records was screened during the 2-week period before administration of the study drug. Information collected included medical history, medications, physical examination, vital signs, weight and height, ECG if not done within the last 4 weeks or if there is known underlying cardiac pathology, and laboratory tests which included hematology (hemoglobin, hematocrit, WBC, MCV, MCH, MCHC, reticulocyte count, platelets, differential count), clinical chemistry (BUN, creatinine, albumin, alkaline phosphatase, total bilirubin, GGT, AST, ALT, LDH, calcium, phosphorus, glucose, bicarbonate, sodium, potassium, chloride), iron studies (serum iron, serum ferritin, total iron binding capacity, percentage serum transferrin saturation), pregnancy test for female subjects if applicable, and hepatitis B test within the last 12 months. Patients were monitored for vital sign abnormalities and adverse events which may be associated with dialysis for three dialysis sessions immediately prior to study drug administration. Monitoring included adverse events which may occur between dialysis sessions. The sponsor's study schedule is attached in Appendix 2.

Patients underwent routine hemodialysis as specified by the Dialysis Center. Within thirty minutes of the start of each dialysis session, 100 mg of Venofer was administered. The following data were collected and recorded at each dialysis session: date; starting time and completion time; body weight [pre- and post-dialysis]; concomitant medication administered during dialysis session; adverse events during dialysis session; dialyser new or re-used; blood loss; time of administration of the study drug; clinical observations; blood pressure and heart rate before the start of the dialysis session, before start of Venofer administration, at 15 minutes, 1 and 2 hours after the start of administration of study drug and at the completion of dialysis; oral temperature before the start of dialysis and at the completion of dialysis. Any serious adverse events after the patient had left the unit were to be reported immediately by the patient and followed up by the investigator. Adverse events between hemodialysis sessions, any additions, or changes to the patient's usual maintenance therapy, during the interim period, were to be documented.

Patients were followed-up at 2 and 5 weeks after the last treatment with Venofer in clinic for clinical evaluation and blood draw for hematological and iron studies.

7.1.1.1.6 Efficacy Parameters

The primary measures of efficacy were number of patients attaining the target blood hemoglobin concentration (≥ 11.0 g/dl) as "responders", and change in hemoglobin

concentration from baseline. Secondary measures of efficacy were changes in serum transferrin saturation [%] and ferritin concentration [ng/ml].

7.1.1.1.7 Safety Assessment

Adverse events were recorded including date and time of onset, severity, relationship to study medication, date of resolution (or the fact that the event is still continuing), action taken, and outcome of the adverse experience. A causality assessment was made by the investigator for every adverse experience as none, unlikely, possibly, and probably related to study drug. The physician was to judge the clinical significance of any laboratory abnormality. If the laboratory value was outside the safety limits and was felt to represent a clinically significant change from the baseline value, an assessment was made as to its drug relatedness and recorded on the Adverse Events (AE) page of the CRF.

7.1.1.1.8 Statistical Methods

The following subsets of populations were to be used for efficacy and safety analyses.

1. ~~Intent-to-Treat~~ (ITT) population: All patients who received at least one dose of study drug.
2. Evaluable population: All patients who satisfy the following criteria: chronic hemodialysis three times weekly, received rHuEPO for at least 4 months with no dosage change for 2 weeks, hemoglobin concentration between 8.0 and 11.0 g/dl for at least 2 consecutive weeks, serum ferritin <300 ng/ml, received all doses of the study drug [1000 mg iron], received no additional iron preparations during study, and completed end of treatment assessment.

Sample size estimation was based on an expected change in hemoglobin levels of 0.5 g/dl with standard deviation of no more than 0.75 g/dl in a two-sided test with 5% significance level. A sample size of 26 was calculated with a power of at least 90%. The sponsor considered that 60 patients were appropriate in this study.

The primary analyses of efficacy were:

1. Ninety-five percent [95%] confidence intervals for the percentage of responders at the end of treatment and the follow-up visits based on the evaluable population.
2. Ninety-five percent [95%] confidence intervals for the change from baseline in hemoglobin at the end of treatment and follow-up visits based on the evaluable population.

The secondary analyses of efficacy were:

Ninety-five percent [95%] confidence intervals for the change from baseline in serum ferritin and serum transferrin saturation at the end of treatment and follow-up visits based on the evaluable population.

All safety analyses were based on the Intent-to-Treat population. Descriptive statistics were to be provided for all safety parameters at each study visit. Ninety-five percent [95%] confidence intervals were to be calculated 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 pretreatment evaluation period.

7.1.1.2 Protocol amendments

Two administrative changes were made to the protocol before patient enrollment had begun.

Administrative change #1, dated December 8, 1998, included protocol clarifications that were deemed necessary as a result of a meeting with investigators. The clarifications were as follows:

- HIV testing for inclusion was optional;
- Study medication was to be kept at temperatures below 25°C (77°C), rather than at room temperature, and it was not to be frozen;
- Clinical chemistry assessments at screening and end of treatment were also to include analysis of sodium, potassium and chloride;
- The last time point for blood pressure and heart rate measurements during dialysis sessions in the treatment period was clarified as at the completion of dialysis rather than at 3 hours after the start of administration of study drug. In addition, oral temperature was to be recorded only before the start of and at the completion of dialysis;
- The change from baseline in hemoglobin concentration was changed from a secondary to a primary efficacy measure.

Administrative change #2, dated February 18, 1999, included protocol clarifications that were requested by the FDA on February 2, 1999 and as follows:

- An intent-to-treat analysis was included in the statistical evaluation of efficacy.
- All additional laboratory results for hemoglobin, serum transferrin and serum transferrin saturation that may have been performed by the investigator in the course of normal medical care while the patient was enrolled in the study were collected and reported.
- The reason for restricting the initiation of Venofer treatment to a Wednesday or Thursday was clarified; it was to avoid blood collection on a weekend day at subsequent treatment visits.

Changes to the Statistical Analysis Plan: Subsequent to finalizing the statistical analysis plan and prior to analyzing the data, the following changes were made to the analysis plan. The changes were needed to define hemoglobin and hematocrit responders based on the NFK-DOQI guidelines. The guidelines state that effective treatment is attainment of hemoglobin level of 11 g/dL or greater; the original statistical analysis plan stated simply greater than 11 g/dL. Similarly, a hematocrit responder was changed from greater than 33% to 33% or greater. All analyses were adjusted accordingly.

7.1.1.3 Historical Control (Van Wyck Study)

The sponsor submitted a study titled "The Natural History of Iron Deficiency in Patients with Dialysis-Associated Anemia" to serve as a historical control for the study LU98001. This study was designed and conducted at a single site at Gambro Health Care Patient Services, Inc., in Tucson, Arizona and approved by the Institutional Review Board of the

University of Arizona. Sixty hemodialysis patients were enrolled in the study and have completed, or are close to completing, up to one year of follow-up at the time of submission. The principal investigator was David Van Wyck, MD. The study protocol and results from the first 10-weeks of the study that corresponded to LU98001 study duration are summarized below:

Study Objectives:

- To determine, in patients without iron supplementation, the natural history of iron deficiency in patients undergoing Epoetin alfa therapy for dialysis associated anemia.
- To explore, in patients without iron supplementation, the relationship between measures of iron status and the dose of Epoetin alfa required to maintain target-range hematocrits.
- To examine the effect of intravenous iron on Epoetin alfa dose requirements in patients with established iron deficiency erythropoiesis.

Study Design: This was a descriptive, prospective study of the natural history of iron deficiency in hemodialysis patients receiving epoetin for dialysis-associated anemia. A total of 60 patients were enrolled and divided into 3 groups according to serum ferritin level at entry: Group 1, less than or equal to 100 ng/ml; Group 2, between 101 and 300 ng/ml, inclusive; and Group 3, between 301 and 1,000 ng/ml. Hemoglobin and hematocrit were to be followed every two weeks and serum ferritin and transferrin saturation were to be followed monthly. Epoetin doses were to be adjusted no more frequently than every 2 weeks. Each adjustment was to be limited to an increase or decrease of 25% of the starting (Day 0) dose. When patients were unable to maintain adequate hematocrit despite a doubling of the entry epoetin dose, treatment with iron dextran was given and the patients were considered to have completed the study.

Study Population:

Inclusion Criteria:

Male and female patients older than 18 years old, able to give informed consent, with a life expectancy greater than 12 months, undergoing hemodialysis three times a week, off intravenous iron for at least 2 weeks prior to study entry, and receiving Epoetin alfa therapy with hematocrit averaging 31-36 for at the three months prior to study entry.

Exclusion Criteria:

Hemoglobinopathy, active infection, use of cytotoxic agents, age less than 18, inability to give informed consent, life expectancy less than one year, Epoetin alfa doses in the month before entry exceeding 36,000 units per week (three times the national average), history of non-compliance with dialysis prescription, demonstrated sensitivity to iron dextran, elective surgery anticipated within one year, or anticipated living related kidney transplantation within one year.

Study Plan:

Assessing body iron status: On Day 0 and at monthly intervals thereafter, body iron status was assessed by serum transferrin saturation, and serum ferritin concentration. Complete

blood counts were performed every other week, including determination of percent hypochromic red cells and percent hypochromic reticulocytes.

Iron administration: If during the study, the adjusted Epoetin dose equaled or exceeded twice the Epoetin dose recorded at study entry, for 4 consecutive weeks, and both the transferrin saturation was less than 50% and the serum ferritin was less than 800 ng/ml, the patient was to receive 5 doses of iv iron dextran, (Dexferum®), American Regent, Shirley, NY), 100 mg/dose on each of five successive dialysis days. Iron status and reticulocyte indices were assessed before iron administration, weekly for four weeks. Four weeks after iv iron administration, the patient was to be considered as completed the study.

Safety assessments were limited to collection of adverse events related to blood loss.

Statistical Methods:

Two patient subsets were defined for analysis in the Van Wyck study: the set of "All-Patients," and a "Matched Cohort" for LU98001 (ferritin levels < 300 ng/mL at entry). Because the study duration in LU98001 trial was approximately 10 weeks, data from Weeks 1- 10 in Van Wyck study patients, during the time when they received no interventions, were used for comparison.

Summary statistics for baseline, for Weeks 2, 4, 6, 8 and 10, and for the last observation on study are presented for observed values and changes from baseline. Paired t-tests were used to assess the statistical significance of the changes from baseline. Ninety-five percent (95%) confidence intervals were constructed and side-by-side boxplots for the various analysis timepoints are presented for each parameter in order to represent both mean changes and variability over time.

Study Results:

Disposition of Patients

Seventeen of the 60 patients had increases of 25% or more in their epoetin dose with or without administration of intravenous iron within the 10 week (73 day) time period. For purposes of comparison, data from these patients were included up to the point of intervention (if any) or 10 weeks (73 days), whichever was earlier. Data for these patients from the time of intervention (earliest intervention in cases where both iron administration and > 25% increase in epoetin dose occurred) were excluded from the analysis. In all cases, an increase in epoetin dose was the reason for exclusion from the analysis, as it was either the earliest or the only intervention that occurred. These patients are listed in the following Table.

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Table 2. Patients With Interventions Resulting in Removal from the Analysis

Patient Number	Baseline Dosage of EPO (U)	New Dosage of EPO (U)	EPO (% Change)	First Dose of Iron (mg)	Days Until Iron Dose*	Days Until $\geq 25\%$ Change in EPO*
0102						
0103						
0104						
0107						
0108						
0117						
0119						
0122						
0126						
0128						
0135						
0136						
0148						
0157						
0158						
0159						
0160						

* Shaded entry indicates reason for patient exclusion from analysis.

Sponsor's table in NDA Vol. 1.20, pp. 26

Demographic and Baseline Characteristics

For the "all-patients" population in the Van Wyck study (see following Table), there were approximately equal numbers of males and females, and mean age was approximately 60 years (40% of the patients were at least 65 years of age). Demographics for the matched cohort were similar except for a preponderance of males (75%).

The matched cohort and "all-patients" population in the Van Wyck study were similar regarding to baseline epoetin dose levels. As expected, the matched cohort showed markedly lower baseline ferritin level.

Table 3. Demographic and Baseline Characteristics

Parameter	History of Iron Deficiency Study (Van Wyck)	
	All-Patients	Matched Cohort
Age (years)	N	60
	Mean	59.9
	SE	1.88
	Median	62
	Min-max	27-84
Age Categories (<65; ≥ 65)	N	60 (100%)
	< 65	36 (60%)
	≥ 65	24 (40%)
Sex	N	60 (100%)
	Female	31 (52%)
	Male	29 (48%)
Epoetin Dose (U)	N	59
	Mean	3498.3
	SE	302.03
	Median	2300
	Min-max	1700-10500
Ferritin Levels (ng/mL)	N	58
	Mean	418.5
	SE	34.96
	Median	406
	Min-max	20-1039

Sponsor's table in NDA Vol. 1.20, pp. 27

Change in Hemoglobin Levels

Overall, for both the all-patients and matched cohort subsets in the Van Wyck study a stable mean hemoglobin was observed during the 10 week period. Slightly decreased hemoglobin was observed started from week 6 to week 10. There was a greater hemoglobin decrease in matched cohort compared to all-patients. The decrease in hemoglobin level from baseline was significant only in Week 6 for both matched cohort and all-patients. The significant mean decrease was attributed to two patients who had marked decreases of 3.7 and 3.2 g/dL at this visit. The patient with the 3.2 g/dL decrease was in the matched cohort. The hemoglobin changes over the time in all-patients and matched cohort are shown in the following tables:

Table 4. Hemoglobin (g/dL) Levels by Visit (All-Patients — Van Wyck)

Visit Window	N	Mean (SE)	Median	Min-Max	95 C.I.	Change Mean (SE)	p-Value
Baseline	60	11.0 (0.09)	11.1	————	10.8, 11.2		
Week 2	53	11.1 (0.11)	11.2	————	10.9, 11.3	0.0 (0.09)	0.952
Week 4	48	11.2 (0.11)	11.3	————	11.0, 11.4	0.1 (0.11)	0.303
Week 6	46	10.8 (0.13)	10.9	————	10.6, 11.1	-0.3 (0.14)	0.036
Week 8	43	11.1 (0.12)	11.1	————	10.9, 11.3	-0.1 (0.13)	0.619
Week 10	37	11.0 (0.13)	11.2	————	10.8, 11.3	-0.1 (0.15)	0.366
Endpoint	55	10.7 (0.14)	11.0	————	10.4, 11.0	-0.3 (0.15)	0.028

p-value: t-test.

Sponsor's table in NDA Vol. 1.20, pp. 28.

Table 5. Hemoglobin (g/dL) Levels by Visit (Matched Cohort — Van Wyck)

Visit Window	N	Mean (SE)	Median	Min-Max	95 C.I.	Change Mean (SE)	p-Value
Baseline	24	11.1 (0.15)	11.2	————	10.8, 11.4		
Week 2	20	11.3 (0.12)	11.2	————	11.1, 11.5	0.1 (0.13)	0.446
Week 4	18	11.3 (0.17)	11.3	————	11.0, 11.6	0.0 (0.21)	0.959
Week 6	18	10.8 (0.23)	11.0	————	10.4, 11.3	-0.6 (0.24)	0.032
Week 8	15	11.4 (0.22)	11.5	————	11.0, 11.8	-0.1 (0.23)	0.801
Week 10	13	10.9 (0.28)	11.2	————	10.4, 11.5	-0.5 (0.32)	0.169
Endpoint	21	10.8 (0.25)	11.2	————	10.3, 11.3	-0.5 (0.29)	0.114

p-value: t-test.

Sponsor's table in NDA Vol. 1.20, pp. 29

In matched cohort, 7 patients were excluded in the analysis because of an increase of EPO dose more than 25% or iron dextran given due to their hemoglobin drop (3 before week 4, 1 at week 4, 1 at week 6, and 2 at week 8). Hemoglobin value was missing in three patients (2 at week 4 and 8, and 1 at week 6). Therefore, only 18 patients were available at week 4 and 15 patients available at week 8 in the matched cohort.

Change in Hematocrit Levels

Overall, the hematocrit levels remained stable over the 10 week period in both all-patients and matched cohort subsets in the Van Wyck study. None of these changes was

statistically significant. Maximum change from baseline was seen at week 6 in both subsets (decrease 0.8% in all patients and 1.2% in matched cohort). This finding was attributed to two patients who had hematocrit decreases of 9.3% and 8.5% at this visit. These were the same patients who exhibited clinically important drops in hemoglobin at this visit. The hematocrit changes over the 10 week period in all-patients and in matched cohort are shown in the following tables.

Table 6. Hematocrit (%) Levels by Visit (All-Patients — Van Wyck)

Visit Window	N	Mean (SE)	Median	Min-Max	95 C.I.	Change Mean (SE)	p-Value
Baseline	60	35.0 (0.34)	35.3	—	34.3, 35.7		
Week 2	53	35.0 (0.43)	35.5	—	34.2, 35.8	-0.4 (0.30)	0.242
Week 4	48	35.7 (0.36)	35.1	—	35.0, 36.4	0.2 (0.40)	0.670
Week 6	46	34.8 (0.41)	34.6	—	34.0, 35.6	-0.8 (0.45)	0.089
Week 8	43	35.7 (0.45)	35.8	—	34.8, 36.6	-0.1 (0.47)	0.906
Week 10	37	36.0 (0.59)	35.8	—	34.8, 37.2	0.4 (0.65)	0.580
Endpoint	55	34.8 (0.53)	35.3	—	33.8, 35.8	-0.5 (0.54)	0.330

p-value: t-test.

Sponsor's table in NDA Vol. 1.20, pp. 31

Table 7. Hematocrit (%) Levels by Visit (Matched Cohort — Van Wyck)

Visit Window	N	Mean (SE)	Median	Min-Max	95 C.I.	Change Mean (SE)	p-Value
Baseline	24	35.2 (0.56)	35.7	—	34.1, 36.3		
Week 2	20	35.5 (0.60)	35.2	—	34.3, 36.7	-0.1 (0.34)	0.808
Week 4	18	35.5 (0.49)	35.2	—	34.5, 36.5	-0.3 (0.65)	0.643
Week 6	18	34.8 (0.79)	34.3	—	33.3, 36.4	-1.2 (0.76)	0.145
Week 8	15	36.5 (0.84)	37.1	—	34.6, 38.2	0.2 (0.86)	0.784
Week 10	13	35.8 (1.18)	35.8	—	33.5, 38.1	-0.4 (1.31)	0.778
Endpoint	21	34.8 (0.87)	35.7	—	33.1, 36.5	-0.8 (0.97)	0.421

p-value: t-test.

Sponsor's table in NDA Vol. 1.20, pp. 32

Changes in Ferritin Levels and Transferrin Saturation

Only 13 patients in all-patients and 5 patients in matched cohort were available at week 8 for ferritin and even fewer patients were available for transferrin saturation. However, there were 20 patients available at endpoint in matched cohort and the mean decrease in ferritin levels at endpoint from baseline was statistically significant (p=0.009). The following tables show the changes in ferritin in both all-patients and matched cohort.

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Table 8. Ferritin Levels (ng/mL) by Visit (All-Patients — Van Wyck)

Visit Window	N	Mean (SE)	Median	Min-Max	95 C.I.	Change Mean (SE)	p-Value
Baseline	58	418.4 (34.96)	406.0	— — —	349.88, 486.92		
Week 2	29	424.8 (54.26)	455.0	— — —	318.45, 531.15	-24.7 (29.31)	0.4066
Week 4	18	397.7 (71.22)	358.5	— — —	258.11, 537.29	24.0 (33.47)	0.4830
Week 6	29	423.0 (59.55)	458.0	— — —	306.28, 539.72	-34.6 (32.83)	0.3011
Week 8	13	385.8 (62.87)	372.0	— — —	262.58, 509.03	-51.7 (20.96)	0.0297
Week 10	19	360.1 (57.67)	414.0	— — —	247.07, 473.13	-39.2 (41.45)	0.3573
Endpoint	49	398.9 (44.09)	389.0	— — —	312.48, 485.32	-29.3 (21.15)	0.1717

p-value: t-test.

Sponsor's table in NDA Vol. 1.20, pp. 34

Table 9. Ferritin Levels (ng/mL) by Visit (Matched Cohort — Van Wyck)

Visit Window	N	Mean (SE)	Median	Min-Max	95 C.I.	Change Mean (SE)	p-Value
Baseline	24	159.5 (17.61)	135.0	— — —	124.98, 194.02		
Week 2	11	132.3 (28.53)	135.0	— — —	76.38, 188.22	2.8 (13.41)	0.8378
Week 4	8	175.4 (34.15)	141.5	— — —	108.47, 242.33	0.3 (16.62)	0.9884
Week 6	11	121.9 (27.09)	102.0	— — —	68.80, 175.00	-14.3 (11.09)	0.2271
Week 8	5	176.4 (37.62)	221.0	— — —	102.67, 250.14	-28.2 (13.10)	0.0978
Week 10	8	115.1 (25.08)	106.5	— — —	65.94, 164.26	-51.5 (15.87)	0.0146
Endpoint	20	126.4 (17.84)	106.5	— — —	91.43, 161.37	-27.6 (9.48)	0.0090

p-value: t-test.

Sponsor's table in NDA Vol. 1.20, pp. 34

For transferrin saturation, it is difficult to make any comparison in matched cohort because few patients were available. The following tables show the changes in transferrin saturation in both all-patients and matched cohort.

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Table 10. Transferrin Saturation (%) by Visit (All-Patients— Van Wyck)

Visit Window	N	Mean (SE)	Median	Min-Max	95 C.I.	Change Mean (SE)	p-Value
Baseline	23	29.0 (2.05)	27.0	—	24.98, 33.02		
Week 2	5	27.4 (4.35)	26.0	—	18.87, 35.93	-2.2 (2.22)	0.3783
Week 4	16	22.3 (1.63)	20.0	—	19.11, 25.50	-5.5 (1.89)	0.0108
Week 6	7	22.4 (1.66)	23.0	—	19.15, 25.65	-6.0 (3.19)	0.1092
Week 8	9	22.1 (2.14)	23.0	—	17.91, 26.29	-3.2 (3.74)	0.4141
Week 10	6	26.8 (4.31)	22.5	—	18.35, 35.25	-0.7 (3.50)	0.8564
Endpoint	21	23.9 (1.57)	23.0	—	20.82, 26.98	-4.4 (2.38)	0.0805

p-value: t-test.

Table 11. Transferrin Saturation (%) by Visit (Matched Cohort — Van Wyck)

Visit Window	N	Mean (SE)	Median	Min-Max	95 C.I.	Change Mean (SE)	p-Value
Baseline	10	28.1 (3.79)	23.5	—	20.67, 35.53		
Week 2	3	29.7 (7.45)	26.0	—	15.10, 44.30	-0.7 (3.38)	0.8620
Week 4	6	20.2 (1.82)	19.5	—	16.63, 23.77	-6.5 (4.40)	0.1999
Week 6	4	21.8 (2.87)	23.0	—	16.18, 27.43	-6.0 (5.67)	0.3677
Week 8	3	19.7 (2.67)	17.0	—	14.47, 24.93	-1.0 (5.13)	0.8635
Week 10	3	24.7 (3.71)	22.0	—	17.43, 31.97	0.3 (6.01)	0.9608
Endpoint	9	22.8 (1.79)	23.0	—	19.29, 26.31	-5.1 (4.31)	0.2696

p-value: t-test.

Sponsor's table in NDA Vol. 1.20, pp. 35

Safety

The safety assessment in historical control was limited to collection of adverse event related to blood loss only. A total of 8 adverse events were recorded including clotted access line/fistula (3), surgery for hip fracture (2), amputation of lower limb (2), and vaginal bleeding (1).

7.1.1.4 Study Results

7.1.1.4.1 Disposition of patients

A total of 77 hemodialysis patients in LU98001 were enrolled at 9 centers to receive 100 mg iron as iron sucrose injection IV during dialysis session for up to 10 sessions. The following table shows the number of patients from each center:

Patient Enrollment by Study Center

Investigators	Study Centers	Number of Patients
K.R. Boren, MD	Boren Research Institute, Mesa, AZ	7
C. Charytan, MD	Nephrology Associate, Flushing, NY	18
M. Cohen, DO, FACP	San Diego Dialysis Services, San Diego, CA	14
M. Kaptan, MD	Nephrology Associates, Nashville, TN	5
W. Klein, MD	Pennsylvania Dialysis Clinic of Reading, Wyomissing, PA	10
N. W. Levin, MD	Yorkville Dialysis Unit, New York, NY	8
J. Roman, MD	Dallas Nephrology Associates, Dallas, TX	2
S. Swann, MD	Total Renal Care, Minneapolis, MN	2
S. Zeig, MD	Fort Lauderdale Inpatient, Fort Lauderdale, FL	11

Reviewer's table

All 77 patients received at least one 100 mg dose of iron as iron sucrose injection and were included in the intent-to-treat population. Seventy-four of the 77 patients (96%) completed the study; 1 patient (1%) received only one dose of 100 mg iron and was discontinued due to an adverse event and 2 patients (3%) were considered discontinued from the study (died) after receiving all 10 doses of iron sucrose injection as they did not complete both follow-up visits. Patient disposition is summarized in the following table:

Table 3 Patient Disposition

	Iron Sucrose Injection — (100 mg IV) ^a
	N (%)
Enrolled Patients	77 (100%)
Intent-To-Treat Patients	77 (100%)
Completed Study ^b	74 (96%)
Discontinued Patients ^b	3 (4%)
Reasons for Discontinuation:	
Adverse event	1 (1%)
Other ^c	2 (3%)

Extracted from Section 9, Table 1.

^a 100 mg iron IV/dialysis session during treatment period.

^b Percents were based on the number of intent-to-treat patients.

^c Other: 2 deaths.

Sponsor's table in NDA Vol. 14.2, pp. 38

7.1.1.4.2 Protocol Deviations

Forty-five patients had deviations from at least one inclusion or exclusion criterion. The most common deviations were TSAT values $\geq 20\%$ (22 patients) and serum ferritin values ≥ 300 ng/mL (16 patients). Deviations from the entrance criteria are summarized in the following table:

Protocol Violations of Inclusion or Exclusion Criteria

Violations	Number of Patients
Violations of the Inclusion Criteria:	
Received r-HuEPO <4 months	4
Epoetin treatment dose did not remain unchanged for 2 weeks	5
Hb was not between 8.0 -11.0 g/dL for at least 2 consecutive weeks	5
TSAT $\geq 20\%$	22
Serum ferritin ≥ 300 ng/mL	16
Serum B12 or folate levels not normal	8
Had infection, malignancy or surgery in the month prior to enrollment	1
Not off all iron supplementation for at least 2 weeks prior to study	6
Received blood transfusion in past 3 months	2
Violations of the Exclusion Criteria:	
Likely to have elective surgery or transplantation within next 6 months	1
Positive test for HIV or hepatitis B	1
Anticipated to require surgery of any kind during the study	1
Used any iron preparation within 2 weeks before blood sampling for screening evaluation	1

Reviewer's table based on sponsor's tables in NDA Vol. 14.2, pp. 39-40

Reviewer's Comments:

Based on the sponsor's data listing available (in NDA Vol. 14.4, pp. 3-15), 42 patients had rHuEPO starting date less than 4 months (120 days), which was much higher than the number listed by the sponsor (4). Also, one patient was not on rHuEPO and one had no record of rHuEPO treatment.

Other protocol deviations are summarized in the following table:

Protocol Deviations	
Protocol Deviations	Number of patients
Did not complete end of treatment assessment	1
Received additional iron preparations during the study	4
Did not receive 1000 mg of study drug	7
Dosing on nonconsecutive dialysis sessions or skipped scheduled dialysis and dosing day	8
Received blood transfusion(s) prior to Day 57 but was not discontinued from the study	2
Missing Day 1 hematology or serum iron indices data, screening records were used for baseline	29
Missing post treatment (end of treatment and/or follow-up) hematology or serum iron indices data	64
Missing screening and end of treatment blood chemistry data	23
Missing screening blood chemistry data	2
Missing end of treatment blood chemistry data	26
At least one blood pressure reading that was >5 minutes from protocol scheduled times	66

Reviewer's table based on sponsor's table in NDA Vol. 14.2, pp. 41-42

7.1.1.4.3 Data Sets Analyzed

All safety analyses were based on the intent-to-treat (ITT) patient population. A patient was included in the ITT population if the patient received at least one dose of study medication. All 77 treated patients were included in the ITT population.

Efficacy analyses were done based on both the evaluable patient population and on the intent-to-treat population. Forty-five of the 77 (58%) patients in the ITT population were considered evaluable. The most common reason for being not evaluable was a screening serum ferritin level ≥ 300 ng/mL (21% of all patients). All reasons for being non-evaluable are summarized in the following table.

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Table 7 Summary of Evaluability and Reasons for Non-Evaluability

	Iron Sucrose Injection (100 mg IV) ^a
	N (%)
All Patients	77 (100%)
Evaluable Patients	45 (58%)
Non-evaluable Patients	32 (42%)
Reasons for Non-evaluability ^b	
Serum ferritin \geq 300 ng/mL	16 (21%)
Did not receive 1000 mg of study drug	7 (9%)
Hb concentration not between 8.0 - 11.0 g/dL for at least 2 consecutive weeks	7 (9%)
Received r-HuEPO for <4 months or had dosage change within 2 weeks	7 (9%)
Received additional iron preparations during study	4 (5%)
Did not complete end of treatment assessments	1 (1%)

Extracted from Section 9, Table 1.

Hb: Hemoglobin.

^a 100 mg iron IV/dialysis session during treatment period.

^b Percents were based on ITT patients. Patients may have had multiple reasons for being non-evaluable. All reasons are summarized; therefore, the total sum of reasons and percents may exceed the total number and percent of non-evaluable patients.

Sponsor's table in NDA Vol. 14.2, pp. 43

7.1.1.4.4 Demographic and Baseline Characteristics

Of the 77 ITT patients who received Venofer, 44 (57%) were male and 33 (43%) were female. The mean age of all patients was 62.5±14.7 years (range: 24-85 years). The greatest proportion of patients were Caucasian (47%) with black (26%) and Hispanic (17%) patients the next most common. The distribution of demographic characteristics in the evaluable population was similar to that in ITT population for sex (60%, 27/45, male and 40%, 18/45, female) race (47%, 21/45, Caucasian, 22%, 10/45, black, and 18%, 8/45, Hispanic) and age (65.0±14.57 years; range: 24-85 years). The following table summarizes patient demographics by sex for ITT and evaluable patients and for all patients combined in each population.

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