

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 21-135**

**STATISTICAL REVIEW(S)**

**STATISTICAL REVIEW AND EVALUATION**

**NDA #: 21-135**

**OCT 17 2000**

**Drug: Venofer (Iron Sucrose Injection)**

**Indication: Treatment of dialysis - associated anemia**

**Sponsor: Luitpold Pharmaceuticals, Inc.**

**Clinical Reviewer: M. Lu, M.D.**

**Statistical Reviewer: Mushfiqur Rashid, Ph.D.**

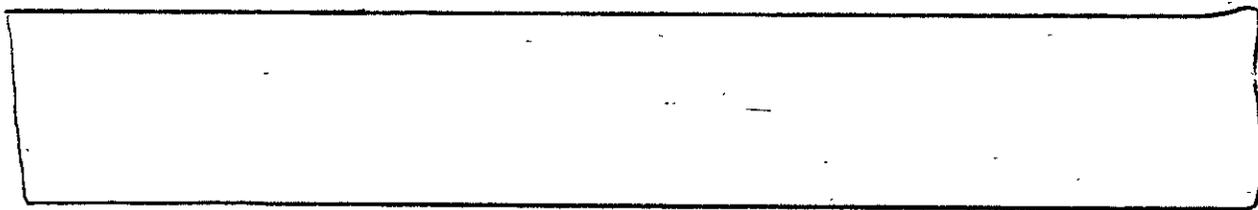
**Documents Reviewed: Volumes 1 - 80, Dated August 6, 1999; Volumes 1- 4, Dated November 16, 1999; Volumes 1- 11, Dated December 7, 1999; Volumes 1-4, Dated July 3, 2000; and submission Dated August 10, 2000**

**User Fee Due Date: November 6, 2000**

**1. INTRODUCTION**

**This submission addresses the efficacy and safety data in support of the intravenous use of Venofer (iron sucrose injection) in dialysis patients**

- 1) with hemodialysis associated anemia (Protocol VENO/BGSA - VIFOR/001);**



**In addition, this submission also contains a historical study (Van Wyck) which is used as a historical control for establishing efficacy of Venofer in protocol LU98001.**

**The rest of this review is organized as follows. Section 1 describes Protocol VENO/BGSA - VIFOR/001. Section 2 contains Protocol LU98002. Section 3 contains LU98001. Section 4 contains Van Wyck study (historical control) along with its comparison with protocol LU98001. Section 5 contains conclusions of this submission.**

## **1. Study VENO/BGSA - VIFOR/001**

A multicenter baseline controlled study conducted in South Africa (van Zyl-Smit et. al, 1977), sponsored by Vifor (International), Inc., serves as the primary study for the determination of the effectiveness of intravenous (IV) iron sucrose (Venofer) in the treatment of anemia in patients with chronic renal failure.

### **Primary Objective:**

To assess the tolerability and safety of intravenous iron sucrose therapy in patients with hemodialysis associated anemia (HDAA).

### **Secondary Objective:**

To assess the efficacy of intravenous iron sucrose therapy with respect to correction of iron deficiency and hematinic response, in patients with HDAA.

### **Original Study Report Objectives:**

This study was designed primarily to assess the tolerability and safety of 100 mg iron as IV iron sucrose therapy in patients with anemic associated with end-stage renal disease (ESRD). However, the efficacy of the therapy in the correction of iron deficiency was also assessed. A report of the study was issued in 1997.

### **Re-analyses Objectives:**

The data from this study were reanalyzed in 1999 by \_\_\_\_\_ for Luitpold Pharmaceuticals, Inc., to verify the results in the original report and also to perform a new analysis to determine the percentage of patients on erythropoietin (EPO) treatment who reached target hemoglobin levels as defined by the National Kidney Foundation Dialysis Outcomes Quality Initiative (NFK-DOQI) Clinical Practice Guidelines. Vifor (International), Inc., authorized Luitpold Pharmaceuticals, Inc., to rely upon this study, and other studies it sponsored discussed in this New Drug Application (NDA).

### **Number and Type of Patients:**

Male and female patients with HDAA, who fulfilled the inclusion criteria, did not meet any of the exclusion criteria, and who gave written informed consent, were included. The sponsor's target was that 100 patients should complete the treatment period. This reviewer could not

locate any sample size determination plan in the protocol.

**Study Duration Per Patient:**

*Treatment period:*

Individual treatment depended on the time needed to administer the total Venofer dose.

*Observation Period:*

Following the treatment period, patients were observed for a month.

**Recruitment Period:**

Patients were included in the study over a six month period, from June 1994 to November 1994.

**Allocation of Patient Numbers:**

Each center was provided with patient numbers in block of 50. A patient was allocated a study number once eligibility for inclusion had been confirmed.

**Study Design:**

Study VENO/BGSA-VIFOR/001, sponsored by Vifor (International), Inc., was an open, single arm, two period (treatment and observation periods) study conducted at five centers in South Africa in which patients served as their own control. The study consisted of a screening period, a treatment period and an observation period. Individual treatment periods depended on the time needed to administer the total dose of Venofer. The total dose was calculated for each patient depending upon baseline predialysis followed the treatment period.

**Dosage:**

*Test dose:* 50 mg Fe (III) i.e. 2.5 ml Venoferrum;

*Maintenance dose:* 100 mg Fe (III) i.e. 5 ml venoferrum

Administered during each hemodialysis session, 2 to 3 times per week. Total Venoferrum dose was determined individually.

**Inclusion Criteria:**

See medical review for inclusion criteria.

**Exclusion Criteria:**

See medical review for exclusion criteria.

### Baseline Demographics

One hundred and thirty-two patients were enrolled in the study. One patient had a blood transfusion 3 days before the test dose and was subsequently withdrawn from the study after the administration of the test dose but before the start of the treatment period. This patient was excluded from all summaries and analyses. The demographics are presented in the following tables.

**Table 1.1: Summary of Patient Demographics (extracted from Table 23, Volume 46 of submission dated August 6, 1999)**

Variable	Male (n=69)	Female (n=69)	Total
<b>Race:</b>			
White	16	14	30
Mixed race	34	30	64
Black	15	16	31
Asian	4	2	6
<b>Age:</b>			
Mean	44.0	38.9	41.6
Range	19.5 - 70.3	16.7-66.9	16.7-70.3
<b>Weight(kg):</b>			
Mean	70.2	63.3	66.9
Range	39.0-116	38.8-117	38.8-117

All 131 patients were included in safety analysis.

### Patient Disposition:

Out of one hundred thirty-two patients were enrolled in the study, 109 patients completed treatment and 23 patients discontinued treatment. Of the 109 patients who completed treatment, 98 completed the observation period and 11 did not complete this period. The disposition of

the enrolled patients during treatment and observation period is described in the following table.

**Table 1.2: Disposition of Patients Enrolled: Number (%) of Patients (extracted from Table 28, Volume 46 of submission dated August 6, 1999)**

	Treatment period	Observation
Total patients enrolled	132	109
Total completed	109	98
Total withdrawn:	23	11
Reason for withdrawal:		
Renal transplant	11	9
Adverse event	5	0
Non-compliance with protocol	2	0
Withdrew consent	1	0
Lost to follow-up	1	1
Received blood transfusion 1 week prior to test dose	1	0
Unexpected worsening of renal pathology, bilateral nephrotomy for reflux	1	0
Patient restarted home dialysis early in error	0	1
Thrombosis of Atrioventricular-fistula	1	0

As mentioned earlier in the study, one patient had a blood transfusion 3 days before the test dose. This patient received only the test dose of iron sucrose and did not receive any study drug during the treatment. Another patient received two days of iron sucrose treatment, but the patient did not have any post baseline data. For the re-analysis, the modified ITT population consisted of 130 patients with post-baseline data. Although 109 patients completed treatment based on the re-analysis, efficacy analyses were based on 105 patients (the same data set in the original report) in order to compare the efficacy results from the original report with the results from the re-analyses. Note that safety analyses were based on 131 patients (the same

data set described in the original protocol report) in order to compare the safety results from the original report with the results from the re-analyses.

#### **Efficacy:**

Hemoglobin, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin (MCHC), serum transferrin saturation, serum ferritin and total iron binding capacity.

#### **Safety:**

The safety endpoints are adverse events, vital signs (temperature, blood pressure and heart-rate), physical examinations, pre-study, interim-study, and post-study hemotological and clinical chemistry profiles.

#### **1.1 Efficacy Results of Study VENO/BGSA-VIFOR/001 (Re-analysis):**

The data from study CENO/BGSA-VIFOR/001 were reanalyzed in February by a Contract Research Organization \_\_\_\_\_ ) for the applicant of this regulatory filing (Luitpold Pharmaceuticals, Inc., Shirley, NY) to insure the integrity of this study. The efficacy results based on the original report were generally comparable to the results based on the re-analysis.

The sponsor's efficacy evaluations were based on hemoglobin, MCV, MCH, MCHC, serum ferritin, red cell ferritin (optional), total iron binding capacity, and serum transferrin saturation. The sponsor analyzed the log-transformed ratio of post study observation (of observation at post study) divided by baseline values by an analysis variance method with patient and period main effects. However, analyses based on log-transformed ratios were not specified in the protocol. Of the 131 patients who received at least one treatment dose of Venofer, one patient did not have post baseline data. If the data were missing for baseline, the screening value was used. There were five patients whose baseline values were missing. For hematology and iron indices data, missing data at post-study were replaced by the last available value for either the observation or treatment period.

The sponsor's analyses of the hematologic and iron data (post-study versus baseline) for modified ITT population (130 patients) are summarized in the following table.

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**Table 1.3: Summary of Hematologic Data (Mean  $\pm$  SD): Post-Study Versus Baseline (extracted from page 45 of sponsor's volume 46, dated August 6, 1999)**

Variable	Observation		
	Baseline (N=130)	Post-study (N=130)	P-value
Hemoglobin, g/dL	7.2 $\pm$ 1.6	8.9 $\pm$ 2.1	<.0001
MCV, fl	89.7 $\pm$ 69.7	89.4 $\pm$ 7.7	.0084
MCH, pg	28.3 $\pm$ 15.7	29.1 $\pm$ 2.8	.0002
MCHC, g/ dL	34.4 $\pm$ 25.8	32.6 $\pm$ 1.7	.8617
Hematocrit, %	22.4 $\pm$ 4.8	27.8 $\pm$ 6.4	<.0001
Serum ferritin, ng/mL	72.3 $\pm$ 65.2	458.6 $\pm$ 364.8	<.0001
Total iron binding capacity, $\mu$ mol/L <sup>c</sup>	53.6 $\pm$ 15.7	43.0 $\pm$ 13.6	<.0001
Serum Transferrin Saturation, %	11.7 $\pm$ 5.5	25.8 $\pm$ 12.3	<0.0001

It is seen from the above table that significant increments in the mean of log-transformed of hemoglobin, hematocrit, serum ferritin, total iron binding capacity and serum transferrin saturation were observed at post study period. No significant increases were observed for MCHC. Note that the sponsor did not give any justification for the use of log-transformed data.

This reviewer conducted Shapiro-Wilk test for checking the normality of the data from ITT (132 patients), MITT (130 patients) and evaluable (105 patients) patient population. It is seen that the variable (post study- baseline) is not normally distributed for evaluable patient population.

This reviewer also conducted paired t test, Sign test and Wilcoxon Signed-Rank test for all three patient populations. The results are summarized in the following table.

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**Table 1.4: Mean Change From Baseline to Post Study in Hemoglobin**

Hemoglobin	N	Observation		Change		P-value		
		Baseline (SEM)	Post-study (SEM)	Mean (SEM)	Median	Sign test	Wilcoxon signed rank test	Paired t test
ITT	132	7.22 (0.136)	8.94 (0.180)	1.71 (0.164)	1.55	0.0001	0.0001	0.0001
MITT	130	7.20 (0.137)	8.94 (0.183)	1.74 (.165)	1.6	0.0001	0.0001	0.0001
Evaluable	105	7.24 (.154)	9.23 (.182)	1.99 (.172)	1.7	0.0001	0.0001	0.0001

It is seen from the above table that the change from baseline to post study period was significantly higher than 0.

#### Subgroup Analyses:

For the primary endpoint, the sponsor performed subgroup analyses with respect to gender, race, age-group and site for the evaluable patient population.

#### Gender

In the following table, we describe an analysis by gender for hemoglobin.

**Table 1.5: Summary of Change From Baseline in Hemoglobin (g/dL) to the End of Treatment Visit by Gender (extracted from sponsor's submission dated November 22, 1999, volume 2, Table 9.1a and 9.1b)**

Gender (n)	Baseline average	End of treatment average	P-value
Male (57)	7.4	9.2	< .0001
Female (48)	7.1	9.2	< .0001

It is seen from the above table that the end of treatment average is significantly increased from baseline average for either sex.

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**Race:**

In the following table, we describe an analysis by race for hemoglobin.

**Table 1.6: Summary of Change From Baseline in Hemoglobin-(g/dL) to the End of Treatment Visit by Race (extracted from sponsor's submission dated November 22, 1999, volume 2, Table 9.1c, 9.1d, 9.1e and 9.1f)**

Race (n)	Baseline average	End of treatment average	P-value
Caucasian (23)	8.0	9.8	<0.0001
Black (24)	6.7	8.8	<0.0001
Coloured (52)	7.1	9.1	<0.0001
Asian (6)	8.1	10.0	<0.0001

It is seen from the above table that the end of treatment average is significantly increased from baseline average for all ethnic groups.

**Age Group**

In the following table, we describe analyses by age-group for hemoglobin.

**Table 1.7: Summary of Change from Baseline in Hemoglobin (g/dL) to the End of Treatment Visit by Age Group (extracted from sponsor's submission dated November 22, 1999, volume 2, Table 9.g, 9.1h and 9.1i)**

Age group (n)	Baseline average	End of treatment average	P-value
< 40 (42)	7.2	9.2	<0.0001
40 - 64 (61)	7.3	9.3	<0.0001
> 65 (2)	8.5	8.9	.2642

It is seen from the above table that the end of treatment average is significantly increased from baseline average among all age groups except age group greater than 65 years.

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**Site**

In the following table, we describe analyses by sites for hemoglobin.

**Table 1.8: Summary of Change from Baseline in Hemoglobin (g/dL) to the End of Treatment Visit by Site (extracted from sponsor's submission dated November 22, 1999, Volume 2, Table 8)**

Site(n)	Baseline average	End of treatment average	P-value
0001 (37)	6.6	8.9	<0.0001
0002 (7)	7.7	9.4	0.0200
0003 (1)	8.2	8.5	
0004 (48)	7.3	9.4	<0.0001
0005(12)	8.6	9.5	0.0334

It is seen from the above table that the end of treatment average is significantly increased from baseline average in all sites except site 0003 (which has only one observation).

Subgroup analyses of change from baseline in hemoglobin (g/dL) to post-study visit were consistent with the change from baseline in hemoglobin (g/dL) to week-2.

## 1.2 Safety Analysis:

### Adverse events:

A total of 131 patients were included in the safety analyses. The only patient excluded from both safety analyses who had only received the test dose of study medication.

The sponsor reported that the most frequent adverse events during the treatment period were hypertension (47% of patients), cramps (37%), and nausea (24%). The sponsor also reported that a minority of these adverse events were possibly related to the study drug. Furthermore, adverse events during the observation period (when no study drug was administered) occurred with similar frequency as during the treatment period. This suggests that treatment with the drug was associated with only a few adverse events, and in fact with no adverse events beyond those that are usually associated with hemodialysis patients with renal failure.

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**Vital Signs:**

The sponsor reported that all vital signs remained essentially unchanged throughout the study.

**Pre-study, Interim-study and Clinical Chemistry profiles:**

The sponsor mentioned that results of all the clinical chemistry variables showed no clinically relevant differences between the pre-study, interim study and post-study clinical chemistry profiles.

**1.3 Conclusions*****Efficacy:***

The efficacy data submitted in this study showed that the change in mean hemoglobin (g/dL) from the baseline to post study was significantly higher than 0.

The sponsor did not perform any formal sample size calculation for this study. This study was designed primarily to assess the tolerability and safety of 100 mg irons as IV iron sucrose therapy in patients with end-stage renal disease (ESRD)-associated with anemia. There was no control group in this study. The patients were used as their own control. In addition, the sponsor did not establish a stable baseline value. Thus, this is not a well controlled study. In order to establish efficacy, a large well designed study with a control group is recommended.

***Safety:***

Although adverse events during the observation period (when no study drug was administered) occurred with similar frequency as during the treatment period, the safety of Venofer cannot be established in the absence of a control group in the trial.

**2. Study LU98002**

The objective of this study was to determine whether Venofer could be safely administered to patients with dialysis-associated anemia who had previously demonstrated anaphylactic reactions to iron dextran. The trial was designed as a descriptive safety study. The efficacy of iron sucrose was also investigated. Detailed descriptions of statistical methods were not provided in the original protocol.

**Design:**

Study LU98002, sponsored by Luitpold Pharmaceuticals, Inc, was a prospective, single arm, open label study in which patients served as their own controls. Patients were enrolled into one of two groups (Groups A and B) at five centers in the United States. Group A patients included patients who had experienced mild anaphylactoid reactions to iron dextran. Group B patients included patients who had experienced severe anaphylaxis to iron dextran (bronchospasm, laryngeal edema, hypertension believed to be due to anaphylaxis, or angioedema, which may require the use of bronchodilators or epinephrine).

**Inclusion Criteria:**

See medical review for inclusion criteria.

**Exclusion Criteria:**

See medical review for exclusion criteria.

**Total Venofer Dose:**

The cumulative dose given during the treatment period was up to 1000 mg. If a patient's serum ferritin exceeded 800 ng/ml or TSAT exceeded 50%, treatment with Venofer was to be discontinued. If the patient tolerated Venofer well, he/she could receive up to 1000 mg of Venofer over 10 dialysis sessions.

**Sample Size Calculation:**

No formal sample size calculation was performed for this study. It was designed as a descriptive safety study.

**Criteria for Evaluations:***Efficacy*

Primary efficacy parameter of hemoglobin (g/dL); and secondary efficacy parameters of hematocrit, serum ferritin, and serum transferrin saturation were assessed.

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**Safety:**

Safety variables assessed included all adverse events, treatment emergent adverse events, serious adverse events, other significant adverse events including anaphylactoid reactions such as: bronchospasm, larungeal edema, hypotension, urticaria and angioedemia.

**Method of Subject Assignment:**

This was a prospective, open label, single arm study. No randomization procedures were required. Each patient enrolled was given a consecutive study number by center by Patients who withdrew from the study were not replaced.

**Subject Population:**

Twenty-three patients (16 in group A and 7 in group B) were enrolled in the study. One patient in group A discontinued from the study (after receiving 5 doses of the study drug) for care of progressive coronary artery disease. The ITT population consisted of 23 patients who received at least one dose of study drug; they were included in the efficacy and safety analyses. The following table presents the demographic and baseline characteristics of the ITT population by group and for all treated patients combined.

**Summary of Patient Demographics**

The patients' demographics are summarized in the following table.

**Table 2.1: Summary of Patient Demographics(extracted from-Table 6, Volume 56 of submission dated August 6, 1999)**

variable	Iron sucrose (100 mg IV)					
	Group A		Group B		All treated patients	
	Male (N=8)	Female (N=8)	Male (N=2)	Female (N=5)	Male (N=10)	Female (N=13)
Age (years): Mean +/- s.d.	50.3±17.6	60.8±16.9	50.0±18.4	46.0±18.9	50.2±16.7	55.1±18.6
Ethnic Origin:						
Caucasian	3	2	1	2	4	4
Black	3	3	1	1	4	4
Asian	0	0	0	1	0	1
Hispanic	2	3	0	1	3	4
Weight (kg) Mean ±sd	85.0±16.8	63.5±16.6	74.1±12.3	58.9±16.0	82.8±16.0	61.7±17.4

## Patient Disposition

A total of 23 hemodialysis patients were enrolled at 5 centers to receive 100 mg iron as iron sucrose IV/dialysis session for up to 10 sessions. Sixteen patients were enrolled in Group A (patients with documented mild anaphylactoid reactions to iron dextran) and 7 in Group B (patients with documented severe anaphylactoid reactions to iron dextran).

All 23 patients received at least one 100 mg dose of iron as iron sucrose and were included in the intent to treat population. Twenty-two (96%) of the 23 patients completed the study; one patient (4%) discontinued the study before receiving 10 doses of iron sucrose. Of the 16 patients in Group A, 15 patients (94%) completed the study and one patient (6%) was discontinued. One patient from Group A withdrew from the study on day 22, after receiving 5 doses of iron sucrose, to obtain further care for progressive coronary artery disease. All group B patients completed the study. Patient disposition is summarized in the following table.

**Table 2.2: Patient Disposition: (extracted from Table 3, Volume 56 of submission dated August 6, 1999)**

	Group A	Group B	All treated patients
	N	N	N
Enrolled patients	16	7	23
Intent to treat patients	16	7	23
Completed Study	15	7	22
Discontinued patients	1	0	1
Reason for Discontinuation	1	0	1
Other			

### 2.1 Efficacy Results:

Table 2.1 summarizes the sponsor's primary efficacy evaluation (hemoglobin) for the ITT population for all patients combined and for patients in group A and in group B separately.

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**Table 2.3: Mean Change From Baseline in Hemoglobin: ITT Population (extracted from Table 7, Volume 56 of submission dated August 6, 1999)**

Variable: hemoglobin	Iron Sucrose (100 mg IV)		
	Group A (N=16)	Group B (N=7)	All Treated Patients (N=23)
Baseline:			
N	15	7	22
Mean +/- SEM	10.61± .225	9.90±0.298	10.38±.19
Median	10.8	10.0	10.50
End of treatment day:			
N	15	7	22
Mean +/- SEM	11.61±.282	11.34±.632	11.52±.27
Median	11.7	11.0	11.65
Change at the end of treatment day (24)			
N	15	7	22
Mean +/- SEM	1.0 ± .21	1.44± .473	1.14 ±.204
Median	1.0	1.5	1.15

It is seen from the above table that a significant (95% confidence interval: 0.72, 1.57 g/dL) increase in the mean hemoglobin was observed from baseline to end of treatment. For all treated patients, sample mean hemoglobin values increase from 10.38 (g/dL) to 11.52 (g/dL).

The administration of ten doses of 100 mg iron as iron sucrose IV/dialysis session also resulted in increasing mean hematocrit (from 32.8% to 36.4%), serum ferritin (from 50.7 ng/mL to 317.0 ng/mL), and serum transferrin saturation (from 14.87% to 23.51%) levels.

Note that there were four patients (out of 23) whose baseline values were missing. These missing baseline values were replaced by the screening values. There was only one patient whose end of treatment value was missing. This patient was not included in the ITT analysis.

This reviewer conducted a paired t test on the change in hemoglobin from baseline to the end of treatment day by discarding the patients whose baseline or end of treatment data were missing. The results are summarized in the following table.

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**Table 2.4: Mean Change From Baseline in Hemoglobin**

Variable	N	Mean (SEM)		Mean Change (SEM)	P-value
		Baseline	End of Treatment		
Hemoglobin	18	10.39 (.1986)	11.30 (.2535)	0.91 (.2008)	0.0003

It is seen that the change in mean hemoglobin (g/dL) from baseline to week-2 treatment period is significantly higher than 0.

#### Subgroup Analyses:

For the primary endpoints, the sponsor performed subgroup analyses with respect to gender, race, age-group and site.

#### Gender:

In the following table, we describe subgroup analyses by gender for hemoglobin.

**Table 2.5: Summary of Change From Baseline in Hemoglobin (g/dL) by Gender (extracted from Table 8, Volume 4 of submission dated November 16, 1999)**

Gender (n)	Baseline average	End of treatment average	Change (95% CI)
Male (10)	10.73	11.73	1.04 (.36, 1.72)
Female (12)	10.09	11.32	1.22 (.59, 1.86)

It is seen from the above table that the iron sucrose injection was significantly effective in increasing the hemoglobin level for either sex.

In the following table, we describe subgroup analyses by race for hemoglobin.

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**Table 2.5: Summary of From Baseline in Hemoglobin (g/dL) by Race (extracted from Table 8, Volume 4 of submission dated November 16, 1999)**

Race (n)	Baseline average	End of treatment average	Change (95% CI)
Caucasian(8)	10.43	11.77	1.34 (.11, 2.58)
Black(8)	10.58	11.46	.89 (.18, 1.59)
Hispanic (6)	10.27	11.62	1.35 (.66, 2.04)
Asian(1)	9.20	9.70	.50

It is seen from the above table that 1000 mg iron doses is effective in increasing hemoglobin level for Caucasian, Black and Hispanic patients.

In the following table, we describe subgroup analyses by age-group for hemoglobin.

**Table 2.6: Summary of From Baseline in Hemoglobin (g/dL) by Race (extracted from Table 8, Volume 4 of submission dated November 16, 1999)**

Age group (n)	Baseline average	End of treatment average	Change (95% CI)
< 40 (5)	9.90	11.50	1.60 (.44, 2.76)
40 - 64 (9)	10.4	11.33	.93 (.12, 1.75)
> 65 (8)	10.66	11.75	1.09 (.36, 1.82)

It is seen from the above table that the change from baseline in hemoglobin is significantly higher than zero for each age-group. This implies that ten doses of 100 mg iron as iron sucrose IV/dialysis session was effective in increasing mean hemoglobin.

In the following table, we describe subgroup analyses by site for hemoglobin.

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**Table 2.7: Summary of Change from Baseline in Hemoglobin (g/dL) by site (extracted from Table 8, Volume 4 of submission dated November 16, 1999)**

Site(n)	Baseline average	End of treatment average	Change (95% CI)
0001 (3)	10.77	12.17	1.40 (0.50, 2.30)
0003 (3)	10.00	10.20	0.2 (-1.5, 1.92)
0004 (7)	10.49	11.87	1.39 (0.71, 2.061)
0005(5)	10.68	11.64	0.96 (-0.61, 2.53)
0006(4)	9.83	11.28	1.45 (-0.54, 3.44)

It is seen from the above table that in two sites (0001 and 0004), the drug was significantly effective in increasing the hemoglobin. The drug showed numerical advantage in the three other sites.

## 2.2 Safety Results:

The sponsor reported that ten of 23 patients (43%) had at least 1 adverse event during the observation period. The sponsor also reported that 18 of 23 patients (78%) had at least one adverse event during the treatment period (treatment emergent adverse events).

### *Treatment Emergent Adverse Events:*

The most common (> 10%) treatment emergent adverse events were those usually associated with renal dialysis including hypotension (35%), asthenia, headache and dizziness (each 17%). Two patients experienced treatment related adverse events (1 pruritus from group A and 1 taste perversion from group B).

In addition, five patients (22%) had adverse events which started in the observation period and which continued through to the treatment period.

The most common (> 10%) treatment emergent adverse events were hypotension (35%), headache, dizziness, and asthenia (each 17%).

The sponsor's summary on treatment emergent adverse events by severity for ITT patients are reported in the following table.

**Table 2.8: All Treatment Emergent Adverse Events by Severity (extracted from Table 5.3.1, Volume 56 of submission dated August 6, 1999)**

		— Iron Sucrose (100 mg/V)		
		Group A (N=16)	Group B (N=7)	All Treated Patients (N=23)
<b>Body System Preferred Term:</b>	<b>Patients with at Least One Adverse Event:</b>	11 (69%)	7 (100%)	18 (78%)
<b>Body as whole:</b>	Asthenia	3 (19%)	1 (14%)	4 (17%)
	Headache	3 (19%)	1 (14%)	4 (17%)
	Pain	2 (13%)	0	2 (9%)
	Injection Site Hemorrhage	0	1 (14%)	1 (4%)
	Sepsis	0	1 (14%)	1 (4%)
<b>Cardiovascular System</b>	Hypotension	4 (25%)	4 (57%)	8 (35%)
<b>Nervous System:</b>	Dizziness	3 (19%)	1 (14%)	4 (17%)
	Anxiety	0	1 (14%)	1 (4%)
	Hypertonia	0	1 (14%)	1 (4%)
<b>Skin and Appendages:</b>	Application site reaction	0	1 (14%)	1 (4%)
	Rash	0	1 (14%)	1 (4%)
	Sweating	0	1 (14%)	1 (4%)
<b>Respiratory System</b>	Dyspnea	0	2 (29%)	2 (9%)
<b>Digestive System</b>	Vomiting	1 (6%)	1 (14%)	2 (29%)
<b>Special Senses</b>	Taste Perversion	0	1 (14%)	1 (4%)
<b>Musculoskeletal System</b>	Leg Cramps	0	1 (14%)	1 (4%)

As there was no control group in this trial, it is not possible to compare these adverse events with a control group.

#### Laboratory Parameters

The sponsor reported that no clinically significant changes were observed in any laboratory parameters except for those hematology parameters related to the efficacy of iron sucrose.

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## 2.3 Conclusions

### *Efficacy:*

The efficacy data submitted in LU98002 showed that the change in mean hemoglobin (g/dL) from baseline to week-2 treatment period was significantly higher than 0. However, the patient population is very small (e.g., 23). These 23 patients were again subdivided: Sixteen patients were enrolled in Group A (patients with documented mild anaphylactoid reactions to iron dextran) and 7 in Group B (patients with documented severe anaphylactoid reactions to iron dextran). The patient population is not homogeneous although the changes from baseline to week-2 treatment period for both groups (Group A and Group B) went to the same direction.

The sponsor did not perform any formal sample size calculation for this study. In fact, the study was designed as a descriptive safety study. There was no control group in this study. The patients were used as their own control. In addition, the sponsor did not establish a stable baseline value. Thus, LU98002 is not a well controlled study.

There is weak evidence that Venofer will be effective in increasing hemoglobin level for patients with dialysis-associated anemia who had demonstrated anaphylactoid reactions to iron dextran. In order to establish an efficacy in this particular population of LU98002, a large well designed study with a control group is recommended.

### *Safety:*

There are more adverse events (43% at least one adverse vents) in the observation period than during the treatment period (78% at least one adverse event). As there was no control group in this study, the sponsor was not able to demonstrate the adequate safety comparison of the Venofer treated patients.

## 3. Study LU98001

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

### *Design:*

This was a Phase II/III, prospective, single arm, open-label study of patients with dialysis-associated anemia. Each patient served as his or her control. At least 72 patients were to be enrolled to obtain 60 evaluable patients. Following screening and a 1-week observation period, single 100 mg doses of iron sucrose injection were administered at each dialysis session either

as a saline diluted slow infusion or as an undiluted slow injection; up to 1000 mg iron was to be administered over 10 consecutive dialysis sessions (over 3 - 4 weeks).

**Study Population:**

Male and female hemodialysis patients with iron deficiency anemia who were at least 18 years of age and who were on epoetin therapy were enrolled in this study.

**Inclusion Criteria:**

See medical review for inclusion criteria.

**Exclusion Criteria:**

See medical review for exclusion criteria.

**Dose:**

100 mg iron as iron sucrose injection/dialysis session.

**Duration of treatment:**

Ten dialysis sessions over 3-4 weeks.

**Sample Size:**

The sponsor mentioned that twenty-six patients were sufficient to detect a difference in hemoglobin levels of 0.5g/dl with a power of at least 90%, if the standard deviation of the change from baseline was not more than 0.75 g/dl in a two sided test with 5% significance level. The number of 60 patients is considered to be appropriate in this study.

**Number of Patients:**

72 (60 evaluable) patients planned/77 enrolled/ 77 analyzed for safety/45 evaluable for efficacy

**Demographic and Baseline Characteristics**

Of the 77 patients who received iron sucrose injection (100 mg iron IV/dialysis session), 44 (57%) were male and 33 (43%) were female. The mean age of all patients was  $62.5 \pm 14.68$  years (range: 24-85 years) and majority of patients were Caucasians (47%), 26% were black and 17% were Hispanics. The majority of patients also had cardiovascular disorders at study entry.

**Table 3.1: Summary of Patient Demographics (extracted from sponsor's submission dated, page 4, Volume 2 Dated December 7, 1999)**

Variable	Male (N=44)	Female (N=33)
Age (years): Mean $\pm$ s.d.	65.3 $\pm$ 14.05	58.8 $\pm$ 14.92
Ethnic Origin:		
Caucasian	24	12
Black	10	10
Asian	3	2
Hispanic	5	8
Other	2	1
Weight (kg) Mean $\pm$ s.d.	80.0 $\pm$ 17.81	75.8 $\pm$ 29.96

**Criteria of Evaluation:**

**Efficacy:**

The primary efficacy parameter of Hb (g/dL) and secondary efficacy parameters of Hct (%), serum ferritin (ng/mL), and serum transferrin saturation (TSAT, %) were assessed at screening, baseline, and end of treatment (Day 24).

The primary efficacy endpoint was the number of hemoglobin responders, defined as patients who attained a target Hb of 11.0 g/dl or greater, and the change from baseline in Hb

concentration, measured at the end of the treatment, 2-week and 5-week follow up visits. For each patient, the treatment was declared effective if the patient was hemoglobin responder at one or more point of these three visits.

### Safety:

Safety variables were assessed included all adverse events, treatment emergent adverse events, and serious adverse events.

### Statistical Methods:

A patient was included in the intent to treat population if the patient received at least 1 dose of study drug. All safety analyses were based on the intent-to-treat. A patient was included in the evaluable population if he or she satisfied the following criteria:

Had chronic hemodialysis 3 times weekly; received r-HuEPO for at least 4 months with no dosage change for 2 weeks; had a hemoglobin concentration between 8.0 and 11.0 g/dL for at least 2 consecutive weeks; had a serum ferritin level <300 ng/mL; received all 10 doses of the study drug (1000 mg iron); received no additional iron preparations during the study; and; completed the end of treatment assessment. The primary and secondary efficacy parameters were analyzed based on both the intent to treat and the evaluable populations.

### 3.1 Efficacy Results

In the following table, we summarize the efficacy results concerning Hb level of 11.0 g/dL.

**Table 3.2: Number and % of Patients Who Attained a Hb Level of 11.0 g/dl (extracted from sponsor's submission dated, page 4, Volume 2 Dated December 7, 1999)**

Visit	N (77)	%	95% Confidence Interval
End of Treatment (Day 24)	41	53%	(41.9%, 64.6%)
2-week follow-up (Day 36)	47	61%	(50.0%, 72.1%)
5-week follow-up (Day 57)	51	66%	(55.5%, 77.0%)

It is seen from the above table that the proportion patients who have Hb level of 11.0 g/dL at the end of the treatment (day 24) is not significantly more than 50% as evidenced by the 95% confidence interval (41.9%, 64.6%). However, the proportion of patients who have level of 11.0 g/dL at the follow-up period (day 36, day 57, etc.) is significantly more than 50% as evidenced by the 95% confidence interval. It is expected that majority of the patients (more than 50%) should have hemoglobin level higher than 11.0g/dL after the Venofer therapy.

In the following table, we summarize the change in mean hemoglobin (g/dL) from baseline to end of treatment period 2-week follow-up period and 5-week follow-up period.

**Table 3.3: Change in Mean Hemoglobin (g/dL) From Baseline to End of Treatment Period in ITT Population (extracted from sponsor's submission dated, page 4, Volume 2 Dated December 7, 1999)**

Visit	baseline	Visit value	Change from baseline
End of treatment-day (Day 24)			
N	69	69	69
Mean $\pm$ SEM	10.3 $\pm$ .12	11.3 $\pm$ .15	1.0 $\pm$ .12
95% CI (g/dL)			[.798, 1.2921]
2-week follow-up (Day 36)			
N	73	73	73
Mean $\pm$ SEM	10.3 $\pm$ .11	11.6 $\pm$ .15	1.3 $\pm$ .14
95% CI (g/dL)			[1.018, 1.571]
5-week follow-up (Day 57)			
N	71	71	71
Mean $\pm$ SEM	10.3 $\pm$ .11	11.5 $\pm$ .17	1.2 $\pm$ .17
95% CI (g/dL)			[.842, 1.505]

If the baseline data were missing, the sponsor used the screening data. Baseline hemoglobin values were missing in 6 patients (7.8%). If any specific visit data were missing, the patient was not included in the analysis for the corresponding visit. There were eight patients whose day 24 data were not available.

This reviewer conducted a paired t test using baseline hemoglobin value and week-2 visit hemoglobin value. The results are summarized in the following table:

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**Table 3.4 (reviewer's): Change in Mean Hemoglobin (g/dL) From Baseline to Week-2 Treatment Period in ITT Population**

Visit	N	Mean (SEM)		Change in Mean (SEM)	p-value
		Baseline	Week-2		
Week-2	69	10.22 (.1223)	11.25 (.1426)	1.27 (.1183)	0.0001

It is seen that the change in mean hemoglobin (g/dL) from baseline to week-2 treatment period is significantly higher than 0.

#### Subgroup Analyses:

For the primary endpoints, the subgroup analyses were performed with respect to gender, race, age-group and site. The subgroup analyses corresponding to the change from the baseline to the end of treatment period are reported in Tables A.1- A.4 in the Appendix. The results of the subgroup analyses were consistent with the results of the primary endpoint of the change from baseline to the end of treatment period.

The subgroup analyses corresponding to the proportion of patients who have Hb level of 11.0 g/dL are summarized below.

#### Gender

The results for the subgroup analysis on gender are summarized in the following table.

**Table 3.5: Summary of Number of Patients Who Attained a Hemoglobin Value Greater Than or Equal to 11.0 g/dL at the End of Treatment by Gender (extracted from Table 8, Volume 10, submitted December 7, 1999)**

Gender	n(%)	Change (95% CI)
Male	26 (59%)	(44.1%, 74.0%)
Female	15 (45%)	(27.8%, 63.1%)

It is seen from the above table that the proportion of patients who have Hb level of 11.0 g/dL at the end of the treatment (day 24) is not significantly more than 50% for either sex.

#### Race

The results for the subgroup analysis by race are summarized in the following table.

**Table 3.6: Summary of Number of Patients Who Attained a Hemoglobin Value Greater Than or Equal to 11.0 g/dL at the End of Treatment by Gender (extracted from Table 8, Volume 10, submitted December 7, 1999) by race**

Race	n(%)	Change (95% CI)
Caucasian	21 (58%)	(41.7%, 75.0%)
Black	9 (45%)	(21.7%, 68.3%)
Hispanic	5 (38%)	(9.1%, 67.9%)
Asian	4 (80%)	(30.3%, 129.7%)

It is seen from the above table that the proportion patients who have Hb level of 11.0 g/dL at the end of the treatment (day 24) is not significantly more than 50% for all ethnic groups.

#### Age

The results for the subgroup analysis by age-group are summarized in the following table.

**Table 3.7: Summary of Number of Patients Who Attained a Hemoglobin Value Greater Than or Equal to 11.0 g/dL at the End of Treatment by Gender (extracted from Table 8, Volume 10, submitted December 7, 1999) by Age Group**

Age group	n (%)	Change (95% CI)
< 40	2 (33%)	(-16.1%, 82.8%)
40 - 64	18 (55%)	(36.9%, 72.2%)
>65	21 (55%)	(38.9%, 71.6%)

It is seen from the above table that the proportion patients who have Hb level of 11.0 g/dL at the end of the treatment (day 24) is not significantly more than 50% for all age groups.

#### Site

The results for the subgroup analyses by site are summarized in the following table.

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**Table 3.8: Summary of Number of Patients Who Attained a Hemoglobin Value Greater Than or Equal to 11.0 g/dL at the End of Treatment by Site (extracted from Table 8, Volume 10, submitted December 7, 1999) by Site**

Site	n (%)	Change (95% CI) —
0001	7 (50%)	(21.1%, 78.9%) --
0002	3(43%)	(-2.9%, 88.6%)
0003	4 (50%)	(8.2%, 91.8%)
0004	1 (50%)	(-399.2%, 499.25)
0005	5 (45%)	(12.0%, 78.9%)
0006	11 (61.1%)	(36.9%, 85.4%)
0007	6 (60%)	(25.0%, 95.0%)
0008	2 (40%)	(-20.8%, 100.8%)
0009	2 (100%)	(100%, 100%)

It is seen from the above table that the proportion patients who have Hb level of 11.0 g/dL at the end of the treatment (day 24) is not significantly more than 50% for all sites except site 0009.

The subgroup analyses corresponding to change in Hb level from baseline are summarized in Appendix.

### 3.2 Safety Analysis:

The sponsor assessed safety variables including adverse events, treatment emergent adverse events, and serious adverse events.

#### Adverse events:

Adverse events reported by at least 2 patients in any study period or continuing across the study are summarized in the following table.

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**Table 3.9: Adverse Events Reported by At Least 2 Patients in a Study Period or Continuing Period by Body System (extracted from sponsor's submission, dated, page 54, Volume 2, Dated December 7, 1999)**

		Iron Sucrose (100 mg/V)		
		Observation Period (N=77)	Continuing (N=77)	Treatment Period (N=77)
Body System Preferred Term	Preferred term for Adverse Event	15(19%)	8 (10%)	52 (68%)
Body as whole:	Pain	0	0	8(10%)
	Abdominal Pain	0	0	6(8%)
	Accidental Injury	0	0	5 (6%)
	Headache	3(4%)	0	4(5%)
	Asthenia	1(1%)	0	2(3%)
	Chest pain	0	0	2(3%)
Cardiovascular System	Hypotension	7 (9%)	0	13(17%)
Nervous System:	Dizziness	0	0	2(3%)
	Hypertension	0	0	4(5%)
	Hypertonia	0	0	2(3%)
Skin and Appendages:	Application site reaction	2(3%)	1(1%)	7(9%)
	Pruritus	1(1%)	0	3(4%)
Respiratory System	Dyspnea	1(1%)	0	3(4%)
	Increase cough	0	2(3%)	1(1%)
	Respiratory Disorder	0	0	2(3%)
Digestive System	Nausea	1(1%)	0	3(4%)
	Diarrhea	0	0	7(9%)
	Constipation	0	0	2(3%)
Metabolic and Nutritional	Peripheral Edema	0	2(3%)	3(4%)
Musculoskeletal System	Leg Cramps	3(4%)	0	4(5%)

It is seen that there were more adverse events by body system during treatment period than the observation period.

***All Treatment Emergent Adverse Events:***

All adverse events which were reported during the observation period and which were reported again during the treatment period with a worsened severity or which were reported only during the treatment period were considered to be treatment emergent adverse events. The sponsor mentioned that fifty of 77 patients (65%) had at least one treatment emergent adverse event. The most common (> 5%) treatment emergent adverse events were hypotension (16%), pain (10%: pain mostly in the arms or legs), diarrhea (9%), abdominal pain, application site reaction (each 8%), and accidental injury.

***Treatment-Related Events:***

Four of the 77 patients (5%) had at least one adverse events considered to be related to study medication. A total of six related adverse events were reported: diarrhea and abdominal pain (1 patients), diarrhea and nausea (1 patient), constipation (1 patient), and taste perversion (1 patient). Only a single related event of diarrhea was considered severe.

***Deaths and Other Serious Adverse Events:***

The sponsor reported that two patients died following the end of treatment with iron sucrose injection but while still enrolled in this study, one of a myocardial infarction and other of coumadin necrosis. Both events were considered by the investigator to be unrelated to study drug. Fourteen patients reported a total of 17 other serious adverse events during the course of this study; 2 severe adverse events reported during the observation period, 5 during or at the end of treatment, and 10 during the follow-up period. The sponsor reported that none of the serious adverse events had relationship with the study medicine.

**3.3 Conclusions**

The efficacy data in this protocol showed the change in mean hemoglobin (g/dL) from baseline to week-2 treatment period is significantly higher than 0. However, the proportion of patients who have Hb level of 11.0 g/dL at the end of the treatment (day 24) is not significantly more than 50% as evidenced by the 95% confidence interval (41.9%, 64.6%).

In Section 4, a comparison of Venofer-treated group (LU98001 study) with a historical group (Van Wyck Study) with respect to the change from baseline will be examined.

***Safety***

All treatment emergent adverse events during the observation period (when no study drug was administered) continued during the treatment period. There are a few treatment related adverse events.

In the absence of a control group, it is not possible to establish the safety of Venofer treated patients.

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#### 4. Van Wyck Study (Historical Control) Versus LU98001

##### 4.1 Van Wyck Study

The Van Wyck study was designed and conducted at a single Gambro Heath Care Patient Services, Inc., site in Tucson, Arizona and approved by the Institutional Review Board of the University of Arizona.

##### Background Information:

**Objectives:** The purpose of the original study was to characterize the natural history of iron deficiency in the patients undergoing erythropoetin therapy without iron supplementation for dialysis associated anemia, and to explore the relationship between iron status and erythropoetin dose requirements.

The objective of this current analysis is to provide a historical control for the study LU98001 submitted by Luitpold Pharmaceuticals, Inc. (Luitpold) in support of Venofer (iron sucrose injection) for the treatment of iron deficiency anemia.

**Design:** This study was designed as a descriptive examination of the natural history of iron deficiency in hemodialysis patients receiving epoetin for dialysis-associated anemia. Inclusion/exclusion required adult hemodialysis patients on epoetin therapy for at least 2 months, and off intravenous iron for at least 2 weeks prior to study entry. The duration of the study for each patient was a variable. Epoetin doses in patients, who were off iron therapy, were adjusted as needed to maintain hematocrits within the Health Care Financing Administration (HFCA)-defined target (31-36%). Beginning on day 0 and at monthly intervals thereafter, body iron status was assessed by determining 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. Epoetin doses were adjusted no more frequently than every 2 weeks. Each adjustment was limited to an increase or decrease of 25% of the starting (Day 0) dose by the same route of administration, in accordance with NKF-DOQI Guidelines. When patients were unable to maintain adequate hematocrits despite a doubling of the entry epoetin dose, treatment with iron dextran was given and the patients were considered to have completed the study. Safety assessments were limited to collection of adverse event related to blood loss.

**Sample Size:** The anticipated sample size was 60 patients, divided into 3 groups according to ferritin levels 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 30 and 1,000 ng/mL.

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### Reasons for Choosing Study LU98001 as a Comparator

The control group chosen was appropriate for comparison to the LU98001 study population for the following reasons:

- 1) both sets of patients were chronic hemodialysis patients,
- 2) inclusion criteria for both studies required that patients were to receive epoetin therapy for at least 2 months,
- 3) patients were required to be off intravenous iron for 2 to 4 weeks prior to screening/baseline,
- 4) patients were enrolled, and all data was collected, prospectively, and
- 5) patients were enrolled during a similar time period (circa 1998-99), and were treated following NKF-DOQI Guidelines.

### Comparisons of Patients Demographics and Baseline Characteristics:

Sixty (60) patients were included in the Van Wyck "All-Patients" group, and a subset of 24 ("Matched Cohort" with respect to LU98001) patients was identified based on ferritin levels at study entry ( $\leq 300$  ng/mL). Comparisons of baseline characteristics of LU98001 study and "Matched-Cohort" of Van Wyck study are summarized in the following table.

**Table 4.1: Comparisons of Baseline Characteristics in Van Wyck Study and LU98001 (extracted from sponsor's Table 12 of Volume 1, July 3, 2000 submission)**

Parameter		LU98001	Van Wyck
Age (years)	N	77	24
	Mean	62.5	56.7
	p-value		.1011
Age Categories ( $< 65$ , $\geq 65$ )	N	77	24
	$< 65$	39(51%)	14(58%)
	$\geq 65$	38(49%)	10 (42%)
	p-value		.641
Sex	N	77	24
	Female	33(43%)	6 (25%)
	Male	44(57%)	18(75%)
	p-value		.152
Epoetin dose (U)	N	75	24
	Mean	7942.7	3312.5
	p-value		0.0001
Ferritin Levels (ng/dL)	N	77	24
	Mean	146.8	159.5
	p-value		.6889

Note: p-values: categorical data: fisher's exact test; Continuous data: ANOVA

It can be seen from Table 4.1 that the patients in the Van Wyck study were approximately equally distributed between males and females, and had a mean age of approximately 60 years (40% of the patients were at least 65 years of age). The only major difference in demographics for the "Matched Cohort" was preponderance of males (75%).

The "Matched-Cohort" and the set of "All-patients" in the Van Wyck study were similar regarding baseline epoetin levels. As expected, the Matched-Cohort had markedly lower baseline ferritin levels, as the selection criteria stipulated that baseline ferritin levels be less than or equal to 300 ng/mL in order to match the baseline ferritin level of LU98001.

#### **Efficacy Endpoints:**

The primary efficacy endpoint in this analysis was change from baseline in mean hemoglobin levels (g/dL). Hemoglobin level changes from baseline were evaluated at Weeks 4, 6, and 8, as well as at endpoint (last observation carried forward). Secondary efficacy variables included hematocrit, serum ferritin, and serum transferrin saturation.

#### **Safety Endpoints:**

Safety endpoints in the LU98001 study included adverse events, blood chemistry, vital signs, and urinalysis. These results are provided comprehensively in the Section 3.

Safety variables in the Van Wyck study are limited to adverse events related to blood loss, as these were the only safety data collected on the case report form.

Because of differences between the two studies in the nature of the safety data collected, the sponsor did not perform any between-study comparison of safety parameters.

#### **Efficacy Analysis**

##### ***Primary Efficacy:***

Table 4.1 provides summary statistics for baseline, for Weeks 2,4,6,8 and 10, and changes from baseline for the "Matched Cohort." Paired t-tests were used to assess the statistical significance of the changes from baseline.

**Table 4.2: Hemoglobin (g/dL) Levels by Visit (Matched Cohort - Van Wyck)**

Visit Window	N	Mean (s.e.)	95% CI	Change Mean (s.e.)	P-value (paired t-test)
Baseline	24	11.1 (0.15)	(10.8, 11.4)		
Week 2	20	11.3 (0.12)	(11.1, 11.5)	0.1 (0.13)	0.446
Week 4	18	11.3 (0.17)	(11.0, 11.6)	0.0 (0.21)	0.959
Week 6	18	10.8 (0.23)	(10.4, 11.3)	-0.6 (0.24)	0.032
Week 8	15	11.4 (0.22)	(11.0, 11.8)	-0.1 (0.23)	0.801
Week 10	13	10.9 (0.28)	(10.4, 11.5)	-0.5 (0.32)	0.169

For the "Matched Cohort" subset, a gradual drift to lower hemoglobin values was observed over the 10 week period analyzed. Mean changes from baseline, except for week 6, were limited to less than 0.3 g/dL. The statistical changes observed were decreases at the 6 week time point relative to study start, in both patient subsets, and the endpoint value in the "All patients" population. This significant mean decrease can be attributed to two patients who had marked decrease of 3.7 and 3.2 g/dL at this visit.

Similar results were found for the "All-Patients" subsets. See Medical Review for details.

### *Secondary Efficacy:*

#### *Hematocrit:*

Table A.5 in the Appendix summarizes the results of the "Matched-Cohort." Similar to the findings for hemoglobin levels, the "Matched Cohort" subsets in the Van Wyck study showed a gradual drift to lower hematocrit over the 10 week period analyzed. Mean changes from baseline (except for week 6) were limited to less than 0.8% in magnitude. None of these changes was statistically significant. Similar trend was observed in the "All Patient" subset.

### *Ferritin and Transferrin*

Table A.6 and Table A.7 in the Appendix summarizes the results of ferritin and serum transferrin levels of the "Matched-Cohort" subset. The number of patients reporting ferritin and transferrin saturation levels varied markedly across visits.

### *Safety Analysis:*

The sponsor mentioned that the safety data recorded in the Van Wyck study was limited to loss adverse events. Adverse events reported by the investigator up to Day 7 were generally bleeding or clotting events associated with fistula or patient access. A small number of other adverse events, Unrelated to the dialysis procedure (e.g., thumb, foot, and toe amputations, coronary artery bypass graft surgery, vaginal bleeding, rectal bleeding) were also reported.

### **4.2 Comparisons LU98001 With Van Wyck Study:**

#### **Study Patients:**

The sponsor made treatment comparisons between the ITT patient population of the LU98001 study (Venofer-treated) and the "All-Patients" and "Matched Cohort" of patients for Van Wyck study.

#### **Primary Efficacy:**

The sponsor mentioned that seventeen (17) of the 60 patients enrolled by Van Wyck in the Natural History of Anemia study had increases in their epoetin dose with or without administration of intravenous iron within 110 week (73 day) time period analyzed in this report. For purpose of comparison, the sponsor used that data from these patients up to the point of intervention (if any) or 10 weeks (73 days), whichever was earlier.

The sponsor used the changes from baseline to Weeks 4, 6, and 8 for non-iron-treated patients in the Van Wyck study to compare to the changes from baseline to Days 4, 36, and 57 for the Venofer treated patents in the LU98001 study. The sponsor used analysis of covariance (ANCOVA) method for these analyses: baseline epoetin dose and the baseline ferritin level were used as covariates.

Table 4.3 summarizes the results of the primary endpoint.

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**Table 4.3: Changes From Baseline in Hemoglobin (g/dL) (Matched - Cohort) (extracted from Table 14 of Volume 1, July 3, 2000 submission)**

Visit Window	Treatment	N	Baseline Mean (se)	Visit Mean (se)	Change Mean (se)	95% CI for Change	p-value (ANCOVA)
Week 4	LU98001	69	10.3(0.12)	11.3(0.15)	1.0(0.12)	(0.77, 1.24)	0.0004
	Van Wyck	18	11.3 (0.16)	11.3 (0.17)	0.0 (0.21)	(-0.41, 0.41)	
Week 6	LU98001	73	10.3 (0.11)	11.6 (0.15)	1.3 (0.14)	(1.03, 1.57)	0.0001
	Van Wyck	18	11.3 (0.15)	10.8 (0.23)	-0.6 (0.24)	(-1.07, -0.13)	
Week 8	LU98001	71	10.3 (0.11)	11.5 (0.17)	1.2 (0.17)	(0.87, 1.53)	0.0001
	Van Wyck	15	11.2 (0.16)	11.4 (0.22)	-0.1 (0.23)	(-0.55, 0.35)	

The Venofer treated patients showed mean increases in hemoglobin levels of approximately 1 g/dL at all visits, in contrast to small, usually negative mean changes for both subsets of untreated patients. The treatment comparisons were statistically significant at all visits. The differences always favored the Venofer treated patients.

For both the "All patients" and "Matched-Cohort" subsets in the Van Wyck study a gradual drift to lower hemoglobin values was observed over the 10 week period analyzed. Mean changes from baseline, except for Week 6, were limited to less than 0.5 g/dL in magnitude although individual patients exhibited occasional larger changes. The only statistically significant changes observed were decreases in the 6 week time point relative to study start, in both patient subsets, and the endpoint value in the "All-Patients" population. This significant mean decrease can be 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 included in the "Matched Cohort."

This reviewer conducted ANCOVA on changes from baseline using baseline hemoglobin, baseline epoetin dose and the baseline ferritin level as covariates. The results are summarized in the following table.

**Table 4.4 (reviewer): Changes From Baseline in Hemoglobin (g/dL) (Matched - Cohort) when baseline hemoglobin, baseline epoetin dose and the baseline ferritin level as covariates**

Visit Window	Adjusted Effect (model based)	p-value
Week 4	0.76	0.0085
Week 6	1.47	0.0001
Week 8	0.85	0.0412

It is seen from the above table that the Venofer treated patient group has significantly more mean hemoglobin change than the historical group for all the visit windows.

This reviewer has also conducted ANCOVA on changes in hemoglobin using the baseline

hemoglobin as a covariate. The results are summarized in the following table.

**Table 4.5 (reviewer): Changes From Baseline in Hemoglobin (g/dL) (Matched - Cohort) when baseline hemoglobin as covariate**

Visit Window	Adjusted Effect (model based)	p-value
Week 4	0.73	0.0112
Week 6	1.43	0.0001
Week 8	0.72	0.0798

It is seen from the above table that Venofer treated patient group has significantly more mean hemoglobin change than the historical group except the week -8 visit window. However, the Week 4 is the main visit window to be considered in this review.

It may be of interest to see an analysis of change of hemoglobin from baseline with out using any covariates. The results are summarized in the following table.

**Table 4.6 (reviewer): Changes From Baseline in Hemoglobin (g/dL) (Matched - Cohort)**

Visit Window	LU98001: Mean		Van Wyck :Mean		Treatment Effect = Mean Change (LU98001) - Mean Change (Van Wyck)	p-value
	Baseline (SEM)	Week-4 (SEM)	Baseline (SEM)	Week-4 (SEM)		
Week 4	10.27 (0.1078)	11.30 (0.1510)	11.23 (0.1563)	11.30 (0.1510)	1.03 (.2663)	0.0002
Week 6	10.27 (.1078)	11.58 (.1493)	11.23 (.1563)	10.79 (.2339)	1.84 (.3034)	0.0001
Week 8	10.27 (.1078)	11.47 (.1709)	11.23 (.1563)	11.39 (.2241)	1.23 (.3780)	0.0016

It is seen from the above table that Venofer treated patient group has significantly more mean hemoglobin change than the historical group in all visit windows.

#### Effect of Age and Sex

Patient subsets based on sex and age (< 65 and > = 65) were created and the impact of these variables assessed. The effect of age and sex on hemoglobin were evaluated. Comparisons between the two studies of the changes from baseline to weeks 4, 6, and 8, in hemoglobin levels were described in the following table.

**Table 4.7: Changes From Baseline in Hemoglobin – Differences Between Studies (extracted from sponsor's Table 22 of Volume 1, July 3, 2000 submission)**

Subset	Week	P-value (ANCOVA)
Men	4	0.0102
	6	0.0002
	8	0.0244
Women	4	0.0285
	6	0.0003
	8	0.0136
< 65 years of age	4	0.0051
	6	0.0001
	8	0.0123
≥ 65 years of age	4	0.0443
	6	0.0066
	8	0.0391

It can be seen from the above table that significant differences between the two studies are evident at all of the time points.

#### Secondary Efficacy:

##### *Hematocrit:*

The results of analysis of change from baseline in hematocrit were very similar to those of the hemoglobin analyses. The results are summarized in the following table.

**Table 4.8: Hematocrit (%) Changes From Baseline by Visit (Matched Cohort) (extracted from Table 16 of Volume 1, July 3, 2000 submission)**

Visit Window	Treatment	N	Baseline Mean (se)	Visit Mean (se)	Change Mean (se)	95% CI for Change	p-value (ANCOVA)
Week 4	LU98001	69	32.1 (0.42)	35.2 (0.51)	3.1(0.37)	(2.36, 3.83)	0.0001
	Van Wyck	18	35.8 (0.57)	35.5 (0.49)	-0.3 (0.65)	(-1.57, 0.97)	
Week 6	LU98001	72	32.4 (0.40)	36.0 (0.53)	3.6 (0.44)	(2.74, 4.46)	0.0001
	Van Wyck	18	36.0 (0.55)	34.8 (0.79)	-1.2 (0.76)	(-2.69, .29)	
Week 8	LU98001	70	32.3 (0.41)	35.6 (0.60)	3.3 (0.54)	(2.24, 4.36)	0.0069
	Van Wyck	15	36.3 (0.61)	36.5 (0.84)	0.2 (0.86)	(-1.49, 1.89)	

Similar to the findings for hemoglobin levels, the "Matched-Cohort" subset (as well as the "All-Patients" subset) in the Van Wyck study showed a gradual drift to lower hematocrit over the 10-week period analyzed.

## *Ferritin and Transferrin Saturation:*

Since the number of patients who reported ferritin and transferrin saturation values varied greatly over visits for the Van Wyck study, the only treatment comparisons were based on the change from baseline to endpoint. The treatment effect was statistically significant for both parameters when comparing the Venofer treated patients versus the untreated all patient and Matched Cohorts. The results were summarized in Table A.8 and table A.9 in the Appendix.

## **Safety Evaluation:**

The sponsor reported that safety data recorded in the Van Wyck study was limited to blood loss adverse events. Adverse events reported by the investigator up to day 73 were generally bleeding or clotting events, unrelated to the dialysis procedure (e.g., thumb, foot, and toe amputations, coronary artery bypass graft surgery, vaginal bleeding, rectal bleeding).

Because of differences between the two studies in the nature of safety data collected, the sponsor could not perform a meaningful between-study comparison of safety.

## **Conclusions:**

The efficacy data submitted in LU98001 and Van Wyck studies showed that Venofer treated patient group has significantly higher change (increase) from baseline in hemoglobin level than Van Wyck study (non- iron treated) patient group.

Because of differences between the two studies in the nature of safety data collected, it was not possible to perform a meaningful between-study comparison of safety.

## **5. Conclusions**

There are three studies (VIFOR/001, LU980002, and LU98001) and one historical analysis (Van Wyck) in this submission. All these studies are within patient studies with patients as their own control. Only part of LU98001 has been compared with the Van Wyck study.

### **5.1 Protocol VIFOR/001**

#### ***Efficacy:***

The efficacy data submitted in this study showed that the change in mean hemoglobin (g/dL) from baseline to post study was significantly higher than 0. This study was designed primarily to assess the tolerability and safety of 100 mg irons as IV iron sucrose therapy in patients with

end-stage renal disease (ESRD) associated with anemia. However, the efficacy of the therapy in the correction of iron deficiency was also assessed. There was no control group in this study. In order to establish a solid efficacy, it would require a large well designed study with a control group.

**Safety:**

Although the adverse events during the observation period (when no study drug was administered) occurred with similar frequency as during the treatment period, in the absence of a control group it is not feasible to conclude that Venofer is a safe drug.

**5.2 Protocol LU98002**

**Efficacy:**

The efficacy data submitted in LU98002 showed that the change in mean hemoglobin (g/dL) from baseline to week-2 treatment period was significantly higher than 0. However, the patient population is very small (e.g., 23).

The sponsor did not perform any formal sample size calculation for this study. In fact, the study was designed as a descriptive safety study. There was no control group in this study. The patients were used as their own control. In addition, the sponsor did not establish a stable baseline value. Thus, LU98001 is not a well controlled study.

There is weak evidence that Venofer will be effective in increasing hemoglobin level for patients with dialysis-associated anemia who had demonstrated anaphylactoid reactions to iron dextran. In order to establish an efficacy in this particular population of LU98002, it would require a large well-designed study with a control group.

**Safety:**

There were more adverse vents (43% at least one adverse vents) ) in the observation period than during the treatment period (78% at least one adverse events). As there was no control group in this study, the sponsor was not able to demonstrate the adequate safety comparison of the Venofer treated patients.

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### 5.3 Protocol LU98001

#### *Efficacy:*

The efficacy data in this protocol showed the change in mean hemoglobin (g/dL) from baseline to week-2 treatment period was significantly higher than 0. However, the proportion of patients who had Hb level of 11.0 g/dL at the end of the treatment (day 24) was not significantly more than 50% as evidenced by the 95% confidence interval (41.9%, 64.6%).

#### *Safety*

All treatment emergent adverse events during the observation period (when no study drug was administered) continued during the treatment period. There are a few treatment related adverse events.

In the absence of a control group, it is not possible to establish the safety of Venofer treated patients.

### 5.4 Protocol LU98001 Versus Van Wyck (Historical Control)

#### *Efficacy:*

The efficacy data submitted in LU98001 and Van Wyck studies showed that Venofer treated patient group has significantly higher change from baseline in hemoglobin level than Van Wyck study (non- iron treated) patient group.

#### *Safety*

Because of differences between the two studies in the nature of safety data collected, it was not possible to perform a meaningful between-study comparison of safety.

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Mathematical Statistician

10/13/00

Concur:  
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HFD-180/ Dr. M. Lu  
HFD-715/ Dr. Nevius  
HFD-715/ Dr. Welch  
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**Table A.1: Summary of Change From Baseline in Hemoglobin (g/dL) to End of Treatment Visit (day 24) by Gender for Study LU98001(extracted from Table 8, Volume 10 of submission dated December, 1999)**

Gender (n)	Baseline average	End of treatment average	Change (95% CI)
Male ( 40)	10.4	11.4	1.0 (0.653, 1.257)
Female ( 29)	10.0	11.2	1.2 (0.735, 1.603)

**Table A.2: Summary of Change From Baseline in Hemoglobin (g/dL) to End of Treatment Visit (day 24) by Race for Study LU98001(extracted from Table 8, Volume 10 of submission dated December 7, 1999)**

Race (n)	Baseline average	End of treatment average	Change (95% CI)
Caucasian (33)	10.3	11.5	1.2 (0.900, 1.488)
Black (18)	10.1	10.9	.8 (0.191, 1.476)
Hispanic (10)	10.3	11.3	0.9 (-0.109, 1.969)
Asian (5)	10.5	11.5	1.0 (0.438, 1.562)

**Table A.3: Summary of Change From Baseline in Hemoglobin (g/dL) to End of Treatment Visit (day 24) by Race for Study LU98001(extracted from Table 8, Volume 10 of submission dated December 7, 1999)**

Age group (n)	Baseline average	End of treatment average	Change (95% CI)
< 40 (3)	10.4	12.0	1.7 (0.013, 3.321)
40 - 64 (31)	10.0	11.1	1.1 (0.727, 1.531)
> 65 (35)	10.5	11.4	.9 (0.578, 1.256)

**Table A.4: Summary of Change From Baseline in Hemoglobin (g/dL) at the End of**

**Treatment Visit (day 24) by Site for Study LU98001(extracted from Table 8, Volume 10 of submission dated December 7, 1999)**

Site(n)	Baseline average	End of treatment average	Change (95% CI)
0001 (9 )	10.6	12.0	1.4 (0.106, 2.694)
0002 (6 )	10.6	11.7	1.1 (0.157, 2.043)
0003 (8 )	10.0	11.0	1.0 (-0.018, 2.043)
0004( 2)	10.5	11.0	.6 (-5.75, 6.953)
0005( 11)	10.2	10.7	0.5 (-0.113, 1.113)
0006(17)	10.4	11.5	1.1 (0.657, 1.419)
0007(10)	9.6	11.0	1.4 (0.654, 2.206)
0008(4)	10.0	10.9	.9 (0.142, 1.658)

**Table A.5: Hematocrit (%) Levels by Visit (Matched Cohort - Van Wyck)**

Visit Window	N	Mean (s.e.)	95% CI	Change Mean (s.e.)	P-value (paired t-test)
Baseline	24	35.2 (0.56)	(34.1, 36.3)	-0.1 (0.34)	
Week 2	20	35.5 (0.60)	(34.3, 36.7)	-0.3(0.65)	0.808
Week 4	18	35.5 (0.49)	(34.5, 36.5)	-1.2(0.76)	0.643
Week 6	18	36.8 (0.84)	(33.3, 36.4)	0.2(0.86)	0.145
Week 8	15	35.8 (1.18)	(34.6, 38.2)	-0.4(1.31)	0.784
Week 10	13	34.8 (0.87)	(33.5, 38.1)	-0.8(0.97)	0.778

**Table A.6: Ferritin Levels (ng/mL) by Visit (Matched Cohort- Van Wyck)**

Visit Window	N	Mean (s.e.)	95% CI	Change in mean (s.e.)	P-value (paired t-test)
Baseline	24	159.5 (17.61)	(124.98, 194.02)		
Week 2	11	132.3 (28.53)	(76.38, 188.22)	2.8 (13.41)	0.8378
Week 4	8	175.4 (34.15)	(108.47, 242.33)	0.3 (16.62)	0.9884
Week 6	11	121.9 (27.09)	(68.80, 175.00)	-14.3 (11.09)	0.2271
Week 8	5	176.4 (37.62)	(102.67, 250.14)	-28.2 (13.10)	0.0978
Week 10	8	115.1 (25.08)	(65.94, 164.26)	-51.5 (15.87)	0.0146

**Table A.7: Transferrin Saturation (%) by Visit (Matched Cohort- Van Wyck)**

Visit Window	N	Mean (s.e.)	95% CI	Mean Change (s.e.)	P-value (paired t-test)
Baseline	10	28.1 (3.79)	(20.67, 35.53)	-0.7 (3.38)	
Week 2	3	29.7 (7.45)	(15.10, 44.30)	-6.5 (4.40)	0.8620
Week 4	6	20.2 (1.82)	(16.63, 23.77)	-6.0 (5.67)	0.1999
Week 6	4	21.8 (2.87)	(16.18, 27.43)	-1.0 (5.13)	0.3677
Week 8	3	19.7 (2.67)	(14.47, 24.93)	0.3 (6.01)	0.8635
Week 10	3	24.7 (3.71)	(17.43, 31.97)	0.3 (6.01)	0.9608

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**Table A.8: Transferrin Saturation (%) at Baseline and Endpoint (Matched Cohort- Van Wyck) (extracted from Table 20 of Volume 1, July 3, 2000 submission)**

Visit Window	Treatment	N	Baseline Mean (s.e.)	Visit Mean (s.e.)	Change in Mean (s.e.)	95% CI for Change	P-value
Endpoint	LU98001	76	17.6 (0.95)	26.4 (1.69)	8.8(1.57)	(5.7, 11.9)	0.0016
	Van Wyck	9	27.9 (4.23)	22.8 (1.79)	-5.1 (4.31)	(-13.6, 3.4)	

**Table A.9: Ferritin Levels (ng/mL) at Baseline and Endpoint (Matched Cohort -Van Wyck) (extracted from Table 18 of Volume 1, July 3, 2000 submission)**

Visit window	Treatment	N	Baseline Mean (s.e.)	Visit Mean (s.e.)	Change	95% CI for change	p-value (ANCOVA)
Endpoint	LU98001	76	146.6 (16.96)	312.0 (33.79)	165.3(24.24)	(117.8,212.8)	0.0001
	Van Wyck	20	153.9 (19.82)	126.4 (17.84)	-27.6 (9.48)	(-46.2, -9.0)	

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