

Table 8 Summary of Patient Demographics: Intent-to-Treat and Evaluable Patients

Variable	Iron Sucrose Injection (100 mg IV) ^a					
	Intent-to-Treat Patients			Evaluable Patients		
	Male (N=44)	Female (N=33)	All Patients (N=77)	Male (N=27)	Female (N=18)	All Patients (N=45)
Age (yrs)						
Mean ± SD	65.3 ± 14.05	58.8 ± 14.92	62.5 ± 14.68	68.0 ± 13.25	60.6 ± 15.69	65.0 ± 14.57
Median	70.5	60.0	64.0	74.0	62.0	69.0
Min, Max	31, 85	24, 83	24, 85	39, 85	24, 83	24, 85
Ethnic Origin ^b						
Caucasian	24 (55%)	12 (36%)	36 (47%)	14 (52%)	7 (39%)	21 (47%)
Black	10 (23%)	10 (30%)	20 (26%)	6 (22%)	4 (22%)	10 (22%)
Asian	3 (7%)	2 (6%)	5 (6%)	3 (11%)	2 (11%)	5 (11%)
Hispanic	5 (11%)	8 (24%)	13 (17%)	4 (15%)	4 (22%)	8 (18%)
Other	2 (5%)	1 (3%)	3 (4%)	0	1 (6%)	1 (2%)
Weight (kg)						
Mean ± SD	80.0 ± 17.81	75.8 ± 29.96		76.4 ± 14.75	70.4 ± 15.98	
Median	78.7	68.5		77.3	67.9	
Min, Max	44, 136	42, 210		44, 103	42, 105	
Height (cm)						
Mean ± SD	171.7 ± 10.05	160.8 ± 6.85		170.3 ± 11.17	160.2 ± 6.76	
Median	172.7	160.0		170.2	159.0	
Min, Max	142, 191	150, 180		142, 191	150, 173	

Extracted from Section 9, Table 2.

SD: Standard Deviation; Min, Max: Minimum, maximum.

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

^b Percents were based on the number of patients in each subset.

Sponsor's table in NDA Vol. 14.2, pp. 44

There were no statistically significant differences between the ITT patients in the LU98001 study and all-patients in historical control with regard to age or sex. The matched cohort patients in historical control were younger and had more males than LU98001 patients but the differences were not statistically significant. Both the all-patients and matched cohort in historical control had significantly lower Epoetin doses at baseline compared to LU98001. The all-patients subset in the historical control had significantly higher ferritin levels but the matched cohort in historical control had a similar ferritin level compared to LU98001. The following table summarizes the results.

APPEARS THIS WAY
ON ORIGINAL

Table 12. Baseline Characteristics (Van Wyck)

Parameter		LU98001	Van Wyck (All-Patients)	Van Wyck (Matched Cohort)
Age (years)	N	77	60	24
	Mean	62.5	59.9	56.7
	SE	1.67	1.88	3.23
	Median	64	62	58.5
	Min-max	24-85	27-84	29-80
	p-value		0.3017	0.1011
Age Categories (<65; ≥ 65)	N	77 (100%)	60 (100%)	24 (100%)
	< 65	39 (51%)	36 (60%)	14 (58%)
	≥ 65	38 (49%)	24 (40%)	10 (42%)
	p-value		0.3030	0.641
Sex	N	77 (100%)	60 (100%)	24 (100%)
	Female	33 (43%)	31 (52%)	6 (25%)
	Male	44 (57%)	29 (48%)	18 (75%)
	p-value		0.3880	0.152
Epoetin Dose (U)	N	75	59	24
	Mean	7942.7	3498.3	3312.5
	SE	611.47	302.03	500.95
	Median	8000	2300	2300
	Min-max	500-32000	1700-10500	1700-10500
	p-value		0.0001	0.0001
Ferritin Levels (ng/mL)	N	77	58	24
	Mean	146.8	418.5	159.5
	SE	16.74	34.96	17.61
	Median	76	406	135
	Min-max	7-552	20-1039	20-291
	p-value		0.0001	0.6889

p-values: Categorical data: Fisher's Exact Test; Continuous data: ANOVA.

Sponsor's table in NDA Vol.-1.20, pp. 37

All-patients (11.0±0.09 g/dl) and matched cohort (11.1±0.15 g/dl) in historical control had a significantly higher hemoglobin level at baseline compared to patients in LU98001 (10.3±0.11 g/dl) (p=0.0001). Similarly, hematocrit in all-patients (35.0±0.34%) and matched cohort (35.2±0.56%) in historical control was also significantly higher than that in LU98001 (32.3±0.39%) (p≤0.0002). For transferrin saturation, only 23 patients in all-patients and 10 patients in matched cohort had baseline value available in historical control. Based on available data, patients in LU98001 (17.5±0.94%) had significantly lower transferrin saturation than all-patients (29.0±2.05%) and matched cohort (28.1±3.79%) in historical control (p≤0.0005).

Medical History/Concomitant Illness

All 77 patients in LU98001 had significant, ongoing medical conditions at entry. The majority of patients (>50%) had genito-urinary, cardiovascular (most commonly hypertension) and endocrine/metabolic concurrent illnesses (including diabetes and hyperphosphatemia).

A total of 32 patients (42%) enrolled had a history of drug allergies and 14 of these patients had multiple drug allergies. Ten patients (13%) reported an allergy or intolerance to iron dextran. While most of the 10 patients with allergies to iron dextran reported itching, urticaria, back pain, low blood pressure and/or chest tightness/pain as allergic symptoms, one patient reported anaphylaxis with laryngeal edema and hypotension, one patient with multiple drug allergies reported blindness and grand mal seizures, one patient reported respiratory distress and hives, one patient reported wheezing, and one patient reported shortness of breath and swelling after iron dextran.

No information on medical history and medication was provided for patients in historical control study.

Physical Examination at Screening (Baseline)

Sixty-five patients (84%) had at least one abnormal finding on physical examination at screening. Abnormalities of the cardiovascular system were most common (51/77 patients, 66%). The most common cardiovascular abnormality on physical examination was systolic ejection murmur \geq II/VI grade (31/77 patients, 40%).

Concomitant Medications/Treatment

Erythropoietin Treatment

Seventy-six of the 77 patients (99%) received intravenous recombinant human erythropoietin (rHuEPO) prior to and during the study period. One patient was reported to have first received rHuEPO on day 32 of the study, however, the inclusion criterion for rHuEPO dosing for >4 months was not indicated as having been violated for this patient. Although patients were to have their rHuEPO doses kept constant during the study, 12 patients (16%) had their rHuEPO dose reduced an average of 39% (range: 8% - 90% of initial dose) from baseline to Day 57, 9 patients (12%) had their rHuEPO dose increased an average of 43% (range: 25-122%) from baseline to Day 57, and 5 patients (6%) had their rHuEPO doses both increased and decreased at some time during the study. Overall, little change in the mean rHuEPO dose was observed; the mean rHuEPO dose was reduced by 1.5% from baseline to Day 57.

Other Concomitant Medications

During the observation period and during the treatment period, all 77 patients (100%) received at least one concomitant medication. The most common ($\geq 20\%$) concomitant medications during the treatment period were antithrombotic agents (75%), calcium (62%), other mineral supplements (normal saline) (60%), combinations of vitamins A and D (52%), beta blocking agents (48%), antacids (40%), drugs for the treatment of peptic ulcer (40%), Nephrocaps (38%), vitamin B 12 and folic acid (30%), selective calcium channel blockers with mainly vascular effects (29%), all agents acting on the renin-angiotensin system (26%), other analgesics and antipyretics (25%), vasodilators used in cardiac diseases (25%), angiotensin converting enzyme (ACE) inhibitors (21%), and insulin (21%). One patient (1%) in the observation period only and 4 (5%) patients during the treatment and/or follow-up period violated the protocol in that they received additional iron preparations.

Reviewer's Comments: Of the 4 patients who received additional iron preparations, 2 patients received Infed (Iron Dextran) injection on follow-up day 27 and follow-up day 55-57, respectively; one patient received oral ferrous sulfate on treatment day 23-24; and one patient received chromagen (oral iron) prior to the study and continued during the study (Based on the sponsor's data in NDA Vol. 14.2, pp. 95 and Vol. 14.4, pp. 3-71).

7.1.1.4.5 Efficacy Results

Efficacy results are summarized for the evaluable population and for the intent-to-treat population. If baseline data were missing, the screening data were used. Baseline hemoglobin values were missing in 6/77 (7.8%) patients and the screening hemoglobin values were used in those patients. If any specific visit data were missing, the patient was not included in the analysis for that visit.

Primary Efficacy Endpoints:

1) Number of patients who attain the target hemoglobin concentration (≥ 11.0 g/dL) at the end of treatment visit, 2-week and 5-week follow-up visits.

Following is the sponsor's table summarizing the number of patients who attained a hemoglobin level of at least 11.0 g/dL by visit day during the study for both populations.

Table 9 Number and Percent of Patients Who Attained a Hemoglobin Value of ≥ 11.0 g/dL: Evaluable and Intent-to-Treat Populations

Visit	Evaluable Patients			Intent-to-Treat Patients		
	N 45	% (100%)	95% Confidence Interval	N 77	% (100%)	95% Confidence Interval
Screening (Day -14 to Day 0)	-	-	-	5	(6%)	-
Day 1 (Baseline)	10	(22%)	-	18	(23%)	-
Day 8	16	(36%)	-	28	(36%)	-
Day 15	19	(42%)	-	35	(45%)	-
Day 22	22	(49%)	-	40	(52%)	-
End of Treatment (Day 24)	27	(60%)	[45.3%, 74.7%]	41	(53%)	[41.9%, 64.6%]
2-Week Follow-up (Day 36)	29	(64%)	[50.1%, 78.8%]	47	(61%)	[50.0%, 72.1%]
5-Week Follow-up (Day 57)	33	(73%)	[60.0%, 86.6%]	51	(66%)	[55.5%, 77.0%]
Treatment Effective*	39	(87%)	[76.5%, 96.9%]	60	(78%)	[68.5%, 87.3%]

Extracted from Section 9, Tables 8.1.1 and 8.1.2.

* Treatment was considered effective if a patient reached the target hemoglobin level at any of the following visits: end of treatment, 2-week follow-up, or 5-week follow-up.

Sponsor's table in NDA Vol. 14.2, pp. 47

Overall, 87% (39/45) of evaluable patients (95% confidence interval: 76.5 - 96.9%) attained a hemoglobin level of ≥ 11.0 g/dl at either end of treatment, 2-week or 5-week follow-up visits. For ITT patients, 78% (60/77 patients, 95% confidence interval: 68.5-87.3%) attained a hemoglobin level of ≥ 11.0 g/dl at either end of treatment, 2-week or 5-week follow-up visits.

Reviewer's Comments: It must be noted that 18 patients had a hemoglobin level ≥ 11.0 g/dl at baseline and 5 patients had a hemoglobin level ≥ 11.0 g/dl at screening. It should also be noted that 15 patients had baseline hemoglobin level between 10.5 and 10.9 g/dl.

An analysis by baseline hemoglobin level in ITT population after excluding 21 patients who had either a screening or a baseline hemoglobin level ≥ 11.0 g/dl was performed by this reviewer.

The following table shows the result:

Number of Patients Who Attained a Hemoglobin Level of ≥ 11.0 g/dl in ITT Population by Baseline Hemoglobin Level after Excluding Patients with Hemoglobin Level ≥ 11.0 g/dl at Baseline or Screening

Baseline Hemoglobin (g/dl)	Number of patients	Patients with Hemoglobin ≥ 11.0 g/dl						
		Treatment				Follow-up		Total*
		Day 8	Day 15	Day 22	End	Day 36	Day 57	
7.3-7.9	3					1	1	2 (66.6%)
8.0-8.9	3						2	2 (66.6%)
9.0-9.4	6			1	1	1	1	4 (66.6%)
9.5-9.9	11		1	2	3	5	5	7 (63.6%)
10.0-10.4	12	3	5	4	6	8	10	11 (91.6%)
10.5-10.9	15	5	9	10	11	11	12	13 (86.6%)
Total	50	8	15	17	21	26	31	36
	100%	16%	30%	34%	42%	52%	62%	72%

*including patients who attained hemoglobin level of ≥ 11.0 g/dl at either the end of treatment, 2-week or 5-week follow-up visits.

Reviewer's table based on sponsor's data in NDA Vol. 14.4, pp. 302-317

From this reviewer's analysis, the number of patients who attained a hemoglobin level of ≥ 11.0 g/dl at either the end of treatment, 2-week or 5-week follow-up was 7/11 (63.2%) in patients with baseline hemoglobin between 9.0 g/dl and 9.5 g/dl, and 24/27 (88.8%) in patients with baseline hemoglobin ≥ 10 g/dl. The number of patients with baseline hemoglobin < 9.5 g/dl were too small to assess. The overall percentage of patients attaining a hemoglobin level of ≥ 11.0 g/dl was 36/50 (72%) in the study population after excluding patients with hemoglobin level ≥ 11.0 g/dl at baseline or screening. The number of patients who attained hemoglobin level ≥ 11.0 g/dl generally increased with time during the study.

2) Change in hemoglobin concentration from baseline:

There was an increase in the mean hemoglobin level from baseline of 1.3 ± 0.17 g/dl (95% CI: 0.94-1.63 g/dL) at end of treatment, 1.6 ± 0.17 g/dl (95% CI: 1.26-1.96 g/dL) at 2-week follow-up, and 1.3 ± 0.2 g/dl (95% CI: 0.88-1.76 g/dL) at 5-week follow-up for evaluable patients. For ITT population, the increase in mean hemoglobin level from baseline was 1.0 ± 0.12 (95% CI: 0.80-1.29) g/dl at the end of treatment, 1.3 ± 0.14 (95% CI 1.01-1.57) g/dl at 2-week follow-up, and 1.2 ± 0.17 (95% CI: 0.84-1.51) g/dl at 5-week follow-up. When measured weekly, a statistically significant (95% CI: 0.09-0.39 g/dl,) mean increase in hemoglobin (0.2 ± 0.07 g/dl) was first observed on Day 8.

The mean change from baseline to each timepoint assessed is summarized in the following sponsor's table for both populations.

APPEARS THIS WAY
ON ORIGINAL

section). An analysis was done by this reviewer for mean change of hemoglobin from baseline by EPO doses change status. The following table shows the results:

**Mean Change in Hemoglobin from Baseline in ITT Population
by EPO Dose Changes during the Study**

EPO Doses	Baseline Mean±SEM*	End-of-Treatment		2-weeks Follow-up		5-weeks Follow-up	
		Visit Mean±SEM	Change Mean±SEM	Visit Mean±SEM	Change Mean±SEM	Visit Mean±SEM	Change Mean±SEM
Constant	10.2±0.1 (n=41)	11.1±0.2 (n=38)	0.98±0.15 (n=36)	11.4±0.2 (n=40)	1.32±0.17 (n=38)	11.3±0.2 (n=38)	1.12±0.23 (n=36)
Decreased	10.6±0.2 (n=13)	11.5±0.3 (n=12)	0.95±0.28 (n=12)	11.8±0.5 (n=12)	1.18±0.35 (n=12)	11.7±0.5 (n=13)	1.05±0.49 (n=13)
Increased	10.2±0.4 (n=8)	10.7±0.3 (n=10)	0.69±0.38 (n=8)	11.0±0.4 (n=10)	1.03±0.45 (n=8)	11.1±0.5 (n=10)	1.04±0.57 (n=8)
Stopped	10.2±0.8 (n=4)	12.7±0.8 (n=4)	2.03±0.55 (n=3)	13.0±0.3 (n=5)	2.63±0.80 (n=4)	12.5±0.5 (n=5)	2.30±0.34 (n=4)
Increased and decreased	11.0±0.4 (n=4)	12.2±0.9 (n=4)	1.20±0.52 (n=4)	12.3±0.7 (n=4)	1.32±0.36 (n=4)	12.2±0.6 (n=4)	1.25±0.46 (n=4)

*SEM: Standard error of the mean

Note: from the sponsor's data listing, 1-patient did not have rHuEPO dose recorded, 44 patients kept the rHuEPO dose constant, 13 patients decreased the rHuEPO dose, 10 increased rHuEPO dose, 4 increased and decreased rHuEPO dose, and 5 stopped rHuEPO during the study (stopped after day 24, 34, 38, 45, 52, respectively).

Reviewer's table based on sponsor's data in NDA Vol. 14.4, pp. 3-15, 302-317

Increases of mean hemoglobin level are seen at end-of-treatment and at 2-week and 5-week follow-up in all groups despite the change of rHuEPO doses during the Venofer treatment.

Secondary Efficacy Parameters

The number of evaluable patients who attained a hematocrit of $\geq 33\%$ was 30/45 (67%, 95% CI: 52.5-80.8%) at the end of treatment visit, 35/45 (78%, 95% CI: 65.3-90.3%) at the 2-week follow-up visit, and 33/45 (73%, 95% CI: 60.0-86.6%) at the 5-week follow-up visit. Results for the intent-to-treat population were very similar to those for the evaluable population.

Significant mean increases in all secondary efficacy measures (hematocrit, serum ferritin and serum transferrin saturation [TSAT]) were observed from baseline to the end of treatment, the 2-week and the 5-week follow-up visits for all evaluable and intent-to-treat patients. In the evaluable population, increases in mean hematocrit levels were noticeable by Day 8 and a maximum increase of $4.7 \pm 0.52\%$ from $32.4 \pm 0.58\%$ to $37.1 \pm 0.65\%$ was seen at the 2-week follow-up. Maximum increase in serum ferritin from 83.6 ± 11.69 ng/mL to 360.3 ± 36.81 ng/mL was seen at the end of treatment visit. Maximum increase in TSAT from $17.1 \pm 1.46\%$ to $27.6 \pm 2.66\%$ was seen at the 5-week follow-up visit. Results for the intent-to-treat patients were similar to those for the evaluable patients for all secondary efficacy measures.

The following table summarizes the mean change from baseline to the end of treatment, the 2-week and 5-week follow-up visits in secondary efficacy variables for evaluable and intent-to treat patients.

Table 11 Mean Changes From Baseline in Secondary Efficacy Variables: Evaluable and Intent-to-Treat Populations

Variable/Visit	Evaluable Patients (N=45)			Intent-to-Treat Patients (N=77)		
	Baseline ^a	Visit Value	Change ^b	Baseline ^a	Visit Value	Change ^b
Hematocrit (%)						
End of Treatment (Day 24)						
N	39	39	39	69	69	69
Mean ± SEM	32.3 ± 0.63	36.0 ± 0.69	3.7 ± 0.49	32.1 ± 0.42	35.2 ± 0.51	3.1 ± 0.37
Min, Max						
95% CI (%)	[2.715, 4.715]			[2.366, 3.842]		
2-Week Follow-up (Day 36)						
N	43	43	43	72	72	72
Mean ± SEM	32.4 ± 0.58	37.1 ± 0.65	4.7 ± 0.52	32.4 ± 0.40	36.0 ± 0.53	3.6 ± 0.44
Min, Max						
95% CI (%)	[3.637, 5.722]			[2.757, 4.507]		
5-Week Follow-up (Day 57)						
N	41	41	41	70	70	70
Mean ± SEM	32.3 ± 0.61	36.0 ± 0.81	3.7 ± 0.74	32.3 ± 0.41	35.6 ± 0.60	3.3 ± 0.54
Min, Max						
95% CI (%)	[2.185, 5.172]			[2.228, 4.372]		
Serum Ferritin (ng/mL)						
End of Treatment (Day 24)						
N	41	41	41	71	71	71
Mean ± SEM	83.6 ± 11.69	360.3 ± 36.81	276.7 ± 30.49	151.7 ± 17.71	456.9 ± 36.21	305.2 ± 25.08
Min, Max						
95% CI (ng/mL)	[215.1, 338.4]			[255.2, 355.3]		
2-Week Follow-up (Day 36)						
N	44	44	44	73	73	73
Mean ± SEM	81.4 ± 11.72	264.2 ± 32.71	182.8 ± 26.23	143.3 ± 16.96	357.1 ± 33.92	213.9 ± 22.63
Min, Max						
95% CI (ng/mL)	[129.9, 235.7]			[168.8, 259.0]		
5-Week Follow-up (Day 57)						
N	41	41	41	68	68	68
Mean ± SEM	86.5 ± 12.47	223.0 ± 28.49	136.5 ± 22.26	147.1 ± 17.46	302.4 ± 34.13	155.4 ± 25.21
Min, Max						
95% CI (ng/mL)	[91.55, 181.5]			[105.0, 205.7]		
TSAT (%)						
End of Treatment (Day 24)						
N	41	41	41	71	71	71
Mean ± SEM	16.9 ± 1.45	25.8 ± 2.05	8.9 ± 1.69	17.6 ± 0.97	26.7 ± 1.57	9.1 ± 1.28
Min, Max						
95% CI (%)	[5.535, 12.36]			[6.581, 11.67]		
2-Week Follow-up (Day 36)						
N	44	44	44	73	73	73
Mean ± SEM	17.3 ± 1.41	25.5 ± 1.46	8.2 ± 1.23	17.5 ± 0.98	25.3 ± 1.33	7.8 ± 1.29
Min, Max						
95% CI (%)	[5.723, 10.67]			[5.230, 10.39]		
5-Week Follow-up (Day 57)						
N	41	41	41	69	69	69
Mean ± SEM	17.1 ± 1.46	27.6 ± 2.66	10.5 ± 2.41	17.5 ± 1.00	26.2 ± 1.74	8.7 ± 1.65
Min, Max						
95% CI (%)	[5.649, 15.40]			[5.424, 12.02]		

Extracted from Section 9, Tables 9.2.1, 9.2.2, 9.3.1, 9.3.2, 9.4.1, 9.4.2.

TSAT: Serum transferrin saturation; CI: Confidence interval; SEM: Standard error of the mean; Min: Minimum; Max: Maximum; %: Percentage; ng/mL: Nanograms/milliliter.

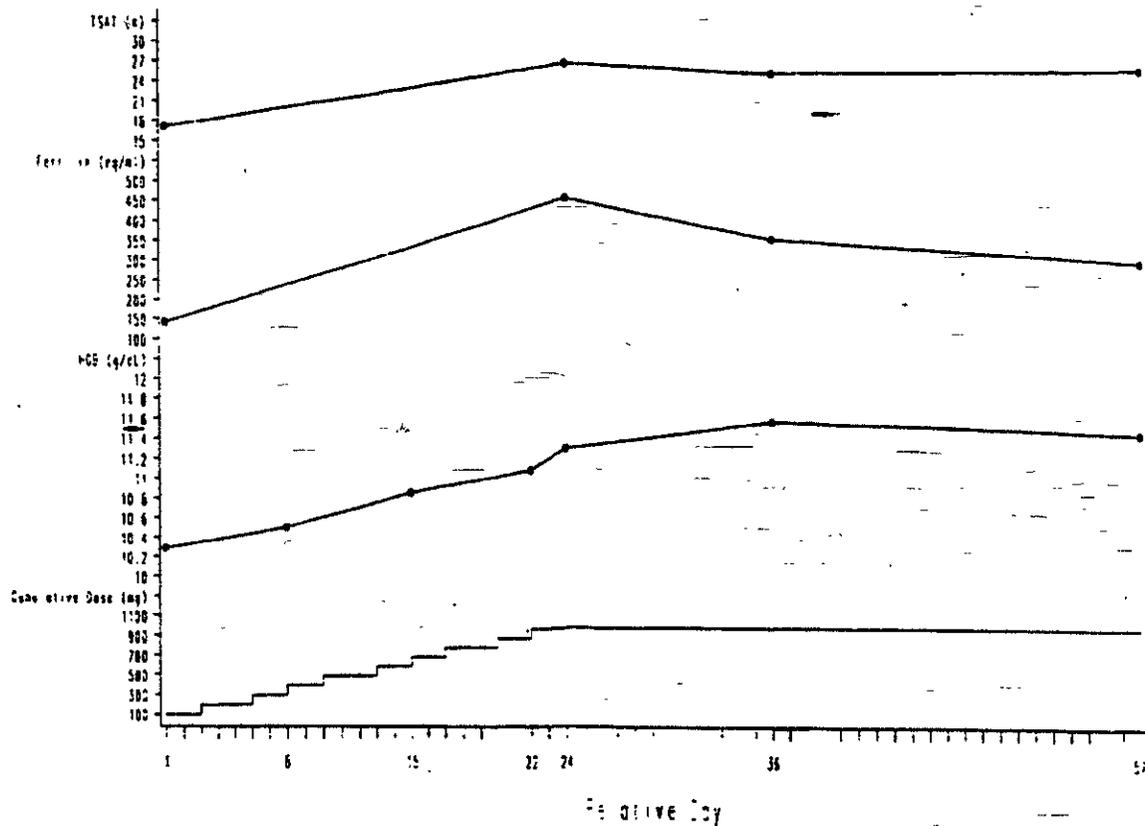
^a Baseline was the assessment taken just prior to the start of study drug administration (Day 1).

^b Change from baseline.

Sponsor's table in NDA Vol. 14.2, pp. 50

Figure A graphic summarizes mean hemoglobin, ferritin and TSAT levels and cumulative iron dose by study day for all intent-to-treat patients.

Figure A: Mean Iron Studies Data and Cumulative Intravenous Iron Dose by Study Day: ITT



Sponsor's figure in NDA Vol. 14.2, pp. 51

Supplemental Efficacy Measures

Serum iron levels increased from a mean of 42.3 ± 2.39 µg/dL at baseline to 57.5 ± 2.90 µg/dL (N=71) at the end of treatment, and from 42.5 ± 2.61 µg/dL at baseline to a maximum mean of 58.8 ± 4.58 µg/dL (N=69) at 5-week follow-up. Total iron binding capacity decreased from a mean of 252.2 ± 8.42 µg/dL at baseline to 224.5 ± 6.46 µg/dL (N=71) at the end of treatment, and from a mean of 255.3 ± 8.30 µg/dL at baseline to a minimum of 219.0 ± 6.00 µg/dL (N=73) at 2-week follow-up. Only the intent-to-treat population was analyzed for these efficacy measures.

7.1.1.4.6 Efficacy Results Compared to Historical Control (Van Wyck Study)

Statistical methods:

Treatment comparisons were made between the ITT patient subset of the LU98001 study and the all-patients and matched cohort of patients in historical control.

Analysis of variance (ANOVA) analysis was used for continuous variables and Chi-square test was used for discrete variables in comparison of demographics and baseline characteristics between LU98001 and historical control.

For efficacy analysis, changes from baseline to Weeks 4, 6, and 8 in historical control (Van Wyck study) were compared to the changes from baseline to Days 24 (end-of-treatment), 36 (2 week follow-up), and 57 (5 week follow-up) in LU98001. In addition, the change from baseline to the last observation was compared between LU98001 and historical control. Analysis of covariance (ANCOVA) with baseline Epoetin dose and the baseline ferritin level as covariates was used for efficacy analysis. The following table shows the comparison in visit window between LU98001 and historical control.

Table 1. Visit Windows

Visit	Visit Window (Study Days)	
	Van Wyck	LU98001
Baseline	Days 0 to 3	Day 1
Week 2	Days 4 to 17	N/A
Week 4	Days 18 to 31	Day 24
Week 6	Days 32 to 45	Day 36 ± 2
Week 8	Days 46 to 59	Day 57 ± 2
Week 10	Days 60 to 73	N/A
Endpoint	Last observation	Last observation

Sponsor's table in NDA Vol. 1.20, pp. 25

Subgroup analyses by sex and age (< 65 and ≥ 65 years) were performed and the impact of these variables was assessed.

Results of Comparison:

Primary Efficacy Parameter - Changes from Baseline in Hemoglobin Values

The following table summarizes the results in LU98001 and in matched cohort in historical control population. The difference in change in mean hemoglobin from baseline between patients in LU98001 and matched cohort in historical control were statistically significant at all visits using ANCOVA analysis with baseline Epoetin dose and the baseline ferritin level as covariates (See Table below).

Table 14. Changes from Baseline in Hemoglobin (g/dL) (Matched Cohort — Van Wyck)

Visit Window	Treatment	N	Baseline Mean (SE)	Visit Mean (SE)	Change Mean (SE)	95 CI for Change	p-value
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	0.0013
	Van Wyck	15	11.5 (0.16)	11.4 (0.22)	-0.1 (0.23)	-0.55, 0.35	
Endpoint	LU98001	76	10.3 (0.11)	11.4 (0.17)	1.2 (0.16)	0.89, 1.51	0.0001
	Van Wyck	21	11.2 (0.16)	10.8 (0.25)	-0.5 (0.29)	-1.07, 0.07	

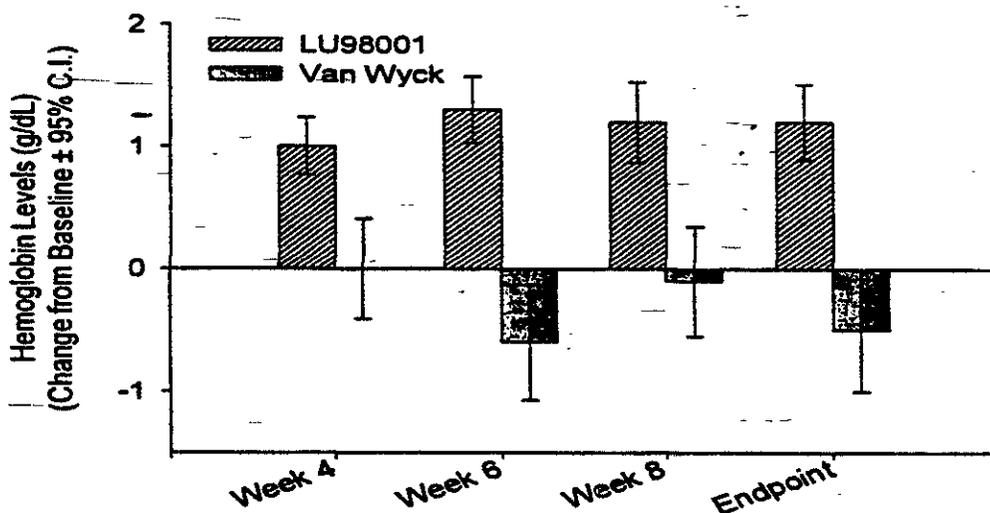
p-values: ANCOVA

Sponsor's table in NDA Vol. 1.20, pp. 39

The differences in changes in mean hemoglobin between LU98001 treatment group and matched historical control remained statistically significant after adding baseline hemoglobin as additional covariate in the ANCOVA analysis ($p=0.0085$ at week 4, $p=0.0001$ at week 6, $p=0.0412$ at week 8, and $p=0.0007$ at endpoint).

The mean changes in hemoglobin from baseline and its 95% CI in LU 98001 and matched cohort in historical control are shown in the following Figure:

Figure 6. Mean Changes from Baseline in Hemoglobin (g/dL)
(Matched Cohort — Van Wyck)



Sponsor's table in NDA Vol. 1.20, pp. 39

The Venofer treated patients also showed mean increases in hemoglobin levels of approximately 1 g/dL at all visits after end-of-treatment in LU98001 compared to small mean decrease in historical control group for all-patients (See Appendix 4).

Secondary Efficacy Parameters

Hematocrit

The mean increase of approximately 3% in hematocrit from baseline in LU98001 at all visits after treatment compared to small increases or decreases in hematocrit at all visits in matched cohort in historical control. These differences between LU98001 and matched cohort in historical control were statistically significant at all visits (See Table below).

APPEARS THIS WAY
ON ORIGINAL

Table 16. Hematocrit (%) Changes from Baseline by Visit (Matched Cohort — Van Wyck)

Visit Window	Treatment	N	Baseline Mean (SE)*	Visit Mean (SE)	Change Mean (SE)	95 CI for Change	p-value
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, 0.29	
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	
Endpoint	LU98001	75	32.3 (0.39)	35.6 (0.58)	3.3 (0.51)	2.30, 4.30	0.0003
	Van Wyck	21	35.6 (0.58)	34.8 (0.87)	-0.8 (0.97)	-2.70, 1.10	

* Baseline varies for each visit due to variation in patients with data at visit.
p-values: ANCOVA.

Sponsor's table in NDA Vol. 1.20, pp. 40

The differences in changes in mean hematocrit between LU98001 treatment group and matched historical control remained statistically significant at week 4 (p=0.002), week 6 (p=0.0003) and endpoint (p=0.009) but not at week 8 (p=0.13), after adding baseline hemoglobin as additional covariate in the ANCOVA analysis.

Ferritin and Transferrin Saturation

Comparison was made of mean change from baseline at endpoint between LU98001 and matched cohort in historical population. The mean increase in ferritin from baseline was 117 ng/ml in LU98001 compared to mean decrease of 46 ng/ml at endpoint in matched cohort in historical population. The difference was highly significant (p=0.001). The mean transferrin saturation was increased 5.7% from baseline in LU98001 compared to the mean decrease of 13.6% in matched cohort in historical population. The difference in mean change was significant (p=0.0016). However, there were only 9 patients available with transferrin saturation result in matched cohort.

Table 18. Ferritin Levels (ng/mL) at Baseline and Endpoint (Matched Cohort — Van Wyck)

Visit Window	Treatment	N	Baseline Mean (SE)*	Visit Mean (SE)	Change Mean (SE)	95 CI for Change	p-value
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	

p-values: ANCOVA.

Table 20. Transferrin Saturation (%) at Baseline and Endpoint (Matched Cohort — Van Wyck)

Visit Window	Treatment	N	Baseline Mean (SE)*	Visit Mean (SE)	Change Mean (SE)	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	

p-values: ANCOVA.

Sponsor's table in NDA Vol. 1.20, pp. 41- 42

The effect of age (<65 years vs. ≥ 65 years) and sex on hematological parameters was evaluated in subgroup analyses. All subgroups (< 65, > 65, men, women) demonstrated significant difference in mean change in hemoglobin between LU98001 and matched cohort in historical population at all visits (Weeks 4, 6, 8, and endpoint).

7.1.1.4.7 Safety Results

All 77 patients in perspective LU98001 study who received at least one dose of study medication were included in the safety analyses.

Extent of Exposure:

Seventy of 77 patients (91%) had 10 dialysis sessions and 10 doses of 100 mg iron as iron sucrose injection IV (1000 mg iron total dose). One patient had only 1 dose of iron sucrose injection before being withdrawn due to an adverse event (gastroenteritis for which the patient was hospitalized), 5 patients had 9 doses and 1 patient had 11 doses of study drug. The mean number of dialysis sessions was 9.8 ± 1.06 during the Venofer treatment period and the total mean dose of Venofer received in study patients was 983.1 ± 105.6 mg iron as iron sucrose injection. Seventy-two patients (94%) received all of their iron sucrose doses undiluted over 5 minutes, 4 patients (all at the same site) received all of their iron sucrose doses diluted in 100 mL 0.9% sodium chloride over approximately 30 minutes, and 1 patient was reported as having received 9 doses undiluted and 1 dose as a diluted dose administered over 5 minutes (no reason was given for this dilution). Two sites (Roman and Zeig, 14 patients) administered the first 1 mL over 1 minute and the final 4 mL of the total 5 mL dose was given 14-15 minutes later.

Adverse Events:

Fifteen of 77 patients (19%) reported at least one adverse event during the observation period and 52 of 77 patients (68%) reported at least one adverse event during the treatment period. In addition, 8 patients (10%) had adverse events which started in the observation period and which continued through to the treatment period. Among all patients, the most common adverse event during the observation period was hypotension (9%). The only adverse events which were continuing from the observation period to the treatment period in 2 or more patients were peripheral edema and increased cough, (each 3%). The most common adverse events in the treatment period (whether or not they were in the observation period or were continuing) were hypotension (17%), pain in extremity (10%), diarrhea, application site reaction (all related to impaired access) (each 9%), abdominal pain (8%), and accidental injury (6%). Only 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 treatment emergent. Only 4 patients had 6 adverse events (abdominal pain, constipation, diarrhea [2 patients], nausea, and taste perversion [minty taste]) that were considered related to the use of study drug.

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

APPEARS THIS WAY
ON ORIGINAL

Table 13 Adverse Events Reported by At Least 2 Patients in a Study Period or Continuing by Body System: Intent-to-Treat Patients

		Iron Sucrose Injection (100 mg IV) ^a		
		Observation Period (N=77)	Continuing ^b (N=77)	Treatment Period (N=77)
Patients With at Least One Adverse Event		15 (19%)	8 (10%)	52 (68%)
Body System	Preferred Term for Adverse Event			
Body as a 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	Hypotension	7 (9%)	0	13 (17%)
Digestive	Diarrhea	0	0	7 (9%)
	Nausea	1 (3%)	0	3 (4%)
	Constipation	0	0	2 (3%)
Metabolic and Nutritional	Peripheral Edema	0	2 (3%)	3 (4%)
Musculoskeletal	Leg Cramps	3 (4%)	0	4 (5%)
Nervous System	Hypertension	0	0	4 (5%)
	Dizziness	0	0	2 (3%)
	Hypertonia	0	0	2 (3%)
Respiratory	Dyspnea	1 (1%)	0	3 (4%)
	Increased Cough	0	2 (3%)	1 (1%)
	Respiratory Disorder	0	0	2 (3%)
Skin and Appendages	Application Site Reaction ^c	2 (3%)	1 (1%)	7 (9%)
	Pruritus	1 (1%)	0	3 (4%)

Extracted from Section 9, Table 5.1.

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

^b An adverse event was counted in the continuing column if it started in the observation period and continued through to the treatment period.

^c All events were clotted/failed access/fistulas

Note: Patients were only counted once in each body system or preferred term. Percents were based on the total number of patients.

Sponsor's table in NDA Vol. 14.2, pp. 54

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 treatment emergent adverse events. Fifty of 77 patients (65%) reported 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 and legs), diarrhea (9%), abdominal pain, application site reaction (each 8%), and accidental injury (6%).

Hypotension was reported as an adverse event only in the observation period (3 dialysis sessions) for 5 patients (6%), in both the observation and the treatment period for 2 patients (3%) and only in the treatment period (10 dialysis sessions) for 12 patients

(16%). For the purposes of reporting adverse events, hypotension was not predefined but was left to the investigator's discretion. There was a lack of consistency of this assessment between investigators and even for individual investigators; however, most of the patients with a decrease in blood pressure reported as an adverse event had a recorded blood pressure drop of >30 mmHg. In both the observation and the treatment periods, these hypotensive events occurred late in the dialysis session, 1-3 hours after the start of dialysis. The majority of patients with hypotension reported as an adverse event were treated with saline for this event. Most of these events were considered mild in severity; only 2 patients had hypotension considered of moderate severity and no events were considered severe. None of these events were considered by the investigators to be related to study drug.

The overall incidence of treatment emergent adverse events was not greater among patients with drug allergies (56%, 18/32) compared to those without allergies (71%, 32/45). Treatment emergent adverse events were reported for 44% (7/16) of patients who received ACE inhibitors during the study and for 70% (43/61) of patients who did not receive this concomitant medication. The following table presents all treatment emergent adverse events reported by at least 2 patients:

Table 14 All Treatment Emergent Adverse Events Reported by at Least 2 Patients by Body System: Intent-to-Treat Patients

		Iron Sucrose Injection (100 mg IV) ^a
		All Patients (N=77)
Patients With at Least One Adverse Event		50 (65%)
Body System	Preferred Term for Adverse Event	
Body as a Whole	Pain	8 (10%)
	Abdominal Pain	6 (8%)
	Accidental Injury	5 (6%)
	Headache	3 (4%)
	Asthenia	2 (3%)
	Chest Pain	2 (3%)
Cardiovascular	Hypotension	12 (16%)
Digestive	Diarrhea	7 (9%)
	Nausea	3 (4%)
	Constipation	2 (3%)
Metabolic and Nutritional	Peripheral Edema	2 (3%)
Musculoskeletal	Leg Cramps	3 (4%)
Nervous	Hypertension	4 (5%)
	Dizziness	2 (3%)
	Hypertonia	2 (3%)
Respiratory System	Dyspnea	2 (3%)
	Respiratory Disorder	2 (3%)
Skin and Appendages	Application Site Reaction	6 (8%)
	Pruritus	2 (3%)

Extracted from Section 9, Table 5.2.

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

Note: Patients were counted only once in each body system or preferred term. Percents were based on the total number of patients.

Sponsor's table in NDA Vol. 14.2, pp. 56.

Treatment Emergent Adverse Events by Severity

Most treatment emergent adverse events for all patients were considered mild (25 patients, 32%) or moderate (19 patients, 25%). Six of 77 patients (8%) had a total of 7 treatment emergent adverse events considered severe: accidental injury, cellulitis, myocardial infarct, diarrhea, thrombocytopenia (one patient each), parathyroid disorder (metastatic calcification due to parathyroid disorder) and coumadin necrosis. All of the treatment emergent adverse events of hypotension were considered mild or moderate in severity.

The overall incidence of severe treatment emergent adverse events was similar in patients with drug allergies (6%, 2/32) compared to those without allergies (9%, 4/45). Severe treatment emergent adverse events rates were: among patients with a history of at least 1 drug allergy (6%, 2/32), with more than 1 drug allergy (14%, 2/14), with only 1 drug allergy (0%, 0/18), and with an allergy to iron dextran (10%, 1/10).

Two of the 16 patients receiving concomitant ACE inhibitors (13%) had severe adverse events (accidental injury and diarrhea) compared with 4 of 61 patients (7%) who were not receiving them.

Treatment Emergent Adverse Events by Causality

Adverse events considered to have a probable, possible, or missing relationship were considered to be related events.

Four of the 77 patients (5%) had at least one adverse event considered to be related to study medication. A total of six related adverse events were reported: diarrhea and abdominal pain, diarrhea and nausea, constipation, and taste perversion. Only a single related event of diarrhea was considered severe. None of the treatment emergent adverse events of hypotension were considered to be related to study medication.

All 4 patients (13%) with treatment-related adverse events were among the 32 patients with a history of at least 1 drug allergy. In the subset of 10 patients with a history of intolerance to iron dextran, 1 patient (10%) had adverse events (diarrhea, nausea) considered related to study drug. In the subset of 18 patients with a history of only 1 drug allergy, 1 patient (6%) reported at least 1 adverse event (taste perversion) considered related to study drug. However, among the 14 patients with more than 1 drug allergy, 3 patients (21%) reported adverse events considered related to study drug (diarrhea, 2 patients, 14%; abdominal pain, constipation, and nausea, each 1 patient, 7%). All of these numbers of patients are small. Only one of these events was severe and caused interruption of treatment with study drug (diarrhea).

Adverse events considered related to study drug were reported for 1 of 16 patients (6%) receiving concomitant ACE inhibitors (diarrhea and nausea, each 6%) compared with 3 of 61 patients (5%) who did not receive them (abdominal pain, taste perversion, constipation, and diarrhea, each 2%). The one patient on ACE inhibitors had multiple drug allergies and had reported blindness and grand mal seizures with iron dextran administration.

Deaths, Other Serious Adverse Events and Other Significant Adverse Events:

Deaths

Two patients died following the end of treatment with iron sucrose injection but while enrolled in this study. The sponsor's narratives of deaths are shown below:

Patient 0002000007

This 56-year-old black male had a significant medical history of ESRD, AV graft, type II diabetes, congestive heart failure with cardiomyopathy, chronic atrial fibrillation, hypertension, anemia, angina, arrhythmia, hyperlipidemia, coronary artery disease, and CVA with no residual effect. Medications at study entry included: calcium carbonate, clonidine, multivitamins, diphenoxylate HCL, quinine sulfate, human insulin, metoprolol, warfarin, nifedipine, phenytoin, digoxin, heparin, gemfibrozil, glipizide, nitroglycerin, calcitriol, epoetin, and furosemide.

The patient received the first dose of iron sucrose injection (100 mg iron IV via the dialysis line) on 27 May 1999 (Study Day 1) and the last dose on 17 June 1999 (Study Day 22). On 18 May 1999 (Study Day-10), the patient was admitted to the hospital after he was found on the floor of his home. On admission to the hospital, the patient's serum glucose was reported to be in the 40s. Treatment in the hospital included evaluation, insulin regimen modification with stabilization of the patient's glucose levels, and instruction on the proper diet and insulin administration. While in the hospital, the patient's hemodialysis access was also evaluated for stenosis. On 23 May 1999 (Study Day-5), the patient was discharged to home in stable condition. On 25 May 1999 (Study Day -3), the patient returned to the dialysis center.

The patient's dialysis notes indicated that the patient was tachycardic, edematous and had wheezing in his lungs. On _____ the patient failed to present for dialysis. Both the patient's residence and emergency contact were called without an answer. The police found the patient deceased and alone at his home. The site reported that there is no definitive cause for the patient's death, although "probable myocardial infarction" was recorded on the adverse event case report form. The investigator commented that the patient had a significant history of heart disease and atrial fibrillation and had been recently symptomatic for tachycardia, hypotension, and edema. The patient also had been experiencing difficulty controlling his glucose levels.

The investigator considered the diabetic insulin reaction to be of moderate severity and the probable myocardial infarction of severe severity and both events unrelated to the study drug.

Patient 0004000002

This 45-year-old black female had a significant medical history of ESRD secondary to glomerulonephritis, cholecystectomy, morbid obesity with sleep apnea and hypoventilation, metabolic acidosis, and allergies to cephalosporin, "coebispenen", and penicillin. Medications at study entry included: warfarin sodium, phosphate binders, nicotine transdermal system, epoetin, and calcium acetate (started on Day -9).

The patient received the first dose of iron sucrose injection (100 mg iron IV via the dialysis line) on 25 February 1999 (Study Day 1) and the last dose on 18 March 1999 (Study Day 22). On 16 March 1999 (Study Day 20), the patient reported left hip pain. Radiography showed metastatic calcification due to parathyroid disorder on 30 March 1999 (Study Day 34). On 20 March 1999 (Study Day 24), the patient's calcium was 9.3 mg/dL and her phosphorous was 7.5 mg/dL. On 1 April 1999 (Study Day 36), the patient was admitted to the hospital and underwent a

parathyroidectomy. On 7 April 1999 (Study Day 42), the event resolved, and the patient was discharged to home in stable condition.

On 15 April 1999 (Study Day 50), the patient was admitted to the hospital with weakness and several complex wounds. She experienced continued weakness and failure to thrive, and had spontaneous hemorrhage from the perineal area which was revealed to be a full thickness skin and muscle necrosis of the perineum and mons pubis. The investigator felt this injury to be related to either coumadin necrosis or calciphylaxis. Subsequently, the patient developed metabolic acidosis, respiratory distress, leukocytosis, and disseminated intravascular coagulation. Dialysis was discontinued, a Do Not Resuscitate status was ordered, and the patient expired. The ESRD Death Notification gives the primary cause of death as septicemia, with warfarin sodium "fasciomyonecrosis" as a secondary cause. The account of this event is per the serious adverse event report.

The investigator considered both events to be of severe intensity and unrelated to study drug.

Other Serious Adverse Events

Fourteen patients reported a total of 17 other serious adverse events (SAEs) during the course of this study; 2 SAEs were reported during the observation period, 5 were reported during or at the end of treatment, and 10 were reported during the follow-up period. None of the serious adverse events were considered by the investigator to have a relationship to study medication. The most common serious adverse events were disorders associated with the application site reaction (3 patients).

The following table summarizes all serious adverse events in this study:

**APPEARS THIS WAY
ON ORIGINAL**

Table 15 Deaths and Other Serious Adverse Events: Intent-to-Treat Patients

Patient Number-Age/Gender	Preferred Term/Description	AE Start Day*/Period	AE Duration (days)	Relationship Severity Action With Study Drug	Treatment and Outcome
0001000011-81/Male	Injection site hemorrhage/ Fistula needle infiltrated and bleeding	20/T	3	None Moderate None	Hospitalized for 1 day, Surgery Recovered
0002000007-55/Male	Hypoglycemic reaction/ Hypoglycemic diabetic insulin reaction	-10/O	7	None Moderate None	Hospitalized Recovered
	Myocardial Infarction/ Probable myocardial infarction	24/F	1	None Severe None	None Died
0003000005-76/Female	Sepsis/ Permacath-related sepsis	22/T	13	None Moderate None	Hospitalized, gentamicin, tobramycin, ciprofloxacin Recovered
0004000002-45/Female	Parathyroid disorder/ Metastatic calcification due to parathyroid disorder	34/F	Continuing	None Severe None	Hospitalized, surgery (parathyroidectomy) Ongoing
	Necrosis/ coumadin necrosis	50/F	4	None Severe None	Medication not reported Died
0005000001-44/Female	Gastroenteritis/ Gastroenteritis	2/T	6	None Moderate Study drug discontinued	Hospitalized, aluminum hydroxide, antibacterials, loperamide, ranitidine; Recovered
0005000004-51/Male	Gastrointestinal hemorrhage/ GI bleed	42/F	5	None Moderate None	PRBCs, cauterization, Recovered
0005000005-39/Male	Pneumonia/ Left lower lobe pneumonia	26/F	5	None Moderate None	Hospitalized, IV vancomycin Recovered
	Pleural effusion/Pleural effusion	26/F	5	None Moderate None	Hospitalized, IV vancomycin Recovered
	Angina pectoris/ Chest pain - angina	62/F	4	None Moderate None	Hospitalized, IV heparin, acetylsalicylic acid, glyceryl trinitrate, oxycodone Recovered

Extracted from Listings 4, 8.2 and 10.4 and serious adverse event reports.

*Days were calculated relative to the start of study medication, such that the first day of study medication was Day 1.

Note: O: Observation period, prior to administration of study drug; T: Iron sucrose treatment period; EOT: End of treatment (Day 24); and F: "Follow-up", Day 24 to Day 57. IV: Intravenous; CHF: congestive heart failure; L: Left; R: Right; GI: Gastrointestinal; PRBCs: Packed red blood cells

Sponsor's table in NDA Vol. 14.2, pp. 59

Table 15 Deaths and Other Serious Adverse Events: Intent-to-Treat Patients (Continued)

Patient Number-Age/Gender	Preferred Term/Description	AE Start Day*/Period	AE Duration (days)	Relationship Severity Action With Study Drug	Treatment and Outcome
0005000007-45/Male	Accidental injury/ (R) hip/(L) femur fracture	27/EOT	29	None Severe None	Hospitalized, surgery Recovered
	Hemorrhagic colitis/ hemorrhagic pseudomembranous colitis	41/F	15	None Moderate None	Hospitalization, surgery, PRBCs, metronidazole, vancomycin Recovered
0005000011-75/Female	Accidental injury/Head injury post fall - probable concussion	25/F	5	None Moderate None	Hospitalized, extra dialysis Recovered
0006000004-76/Male	Cellulitis/(L) arm cellulitis	2/T	68	None Severe None	Hospitalized, morphine, IV sodium ampicillin/sulbactam, IV vancomycin Recovered
0006000005-64/Male	Congestive heart failure/CHF, fluid overload	40/F	4	None Moderate None	Hospitalized, dialysis Recovered
0006000011-51/Female	Application site reaction/clotted access	41/F	4	None Moderate None	Hospitalized Recovered
0006000012-50/Female	Infection/Infected pilonidal cyst - hospital	-4/O	4	None Moderate None	Hospitalized, incision and drainage, IV cefazolin, ciprofloxacin, IV gentamicin, IV vancomycin Recovered
0006000013-70/Male	Application site reaction/clotted fistula	31/F	32	None Moderate None	Hospitalized, surgical repair Recovered

Extracted from Listings 4, 8.2 and 10.4 and serious adverse event reports.

* Days were calculated relative to the start of study medication, such that the first day of study medication was Day 1.

Note: O: Observation period, prior to administration of study drug; T: Iron sucrose treatment period; EOT: End of treatment (Day 24); and F: "Follow-up", Day 24 to Day 57. IV: Intravenous; CHF: congestive heart failure; L: Left; R: Right; GI: Gastrointestinal; PRBCs: Packed red blood cells.

Sponsor's table in NDA Vol. 14.2, pp. 60.

Discontinuations Due to Adverse Events

One patient was discontinued from this study due to an adverse event. On Day 2, following the first dose of study drug, patient was hospitalized for 6 days due to gastroenteritis, an event considered unrelated to study drug. The patient was discontinued from the study on Day 8.

Administration of study drug was interrupted for 4 patients due to adverse events: a mild application site reaction (1 day delay from Day 15 to Day 16), mild malaise (skipped

dosing day from Day 1 to Day 6), severe diarrhea (skipped dosing day from Day 17 to Day 22), and moderate diarrhea and abdominal pain (skipped dosing day from Day 3 to Day 8). One additional patient was dialyzed in the hospital while having a fistula repaired, and missed the second dose of study drug on Day 3. Only one of these adverse events was considered related to study drug, the severe diarrhea.

Other Medically Important Events

Patients who had bronchospasm, as evidenced by dyspnea and wheezes; laryngeal edema, as evidenced by stridor with or without edema; hypotension, as evidenced by a fall in systolic BP > 30 mmHg; urticaria; and/or angioedema within the first hour of administration of study drug that were considered by the investigator to have been related to study drug could be considered to have had an acute anaphylactoid reaction to IV iron sucrose.

The sponsor stated that no patient in this study had symptoms of an anaphylactoid reaction. Of the 10 patients with a history of allergy/intolerance to iron dextran, 5 patients (50%) experienced at least one adverse event during treatment with intravenous iron sucrose injection; only 1 of these patients (10%) had adverse events (2) considered related to study drug. One of the patients with a history of intolerance to iron dextran (blindness and grand mal seizures with iron dextran) was the only patient with a history of drug allergies who had adverse events considered possibly related to study medication (severe diarrhea on Day 17 and moderate nausea on Day 24); treatment with study drug was interrupted due to the diarrhea. This patient also reported pruritus on Day 1, an event considered by the investigator to be moderate in intensity and to have an unlikely relationship to study drug. The patient with a history of anaphylaxis to iron dextran (laryngeal edema and hypotension with iron dextran) experienced asthenia on Day 13 and left hand pain on Day 15, both considered mild and unrelated to study drug. The patient with respiratory distress to iron dextran had no adverse event with iron sucrose injection and the patient with shortness of breath after iron dextran had a fistula infection during the treatment period and pneumonia with pleural effusion during the follow-up period, all considered unrelated to iron sucrose injection.

Reviewer's Comments: Monitoring for anaphylactoid reaction within the first hour of drug administration was not described in study protocol. Based on the sponsor's data, the types of allergy/intolerance reactions to iron dextran in the 10 patients were itching and lower blood pressure (2), urticaria (4), laryngeal edema (1), swelling (unclear location) and shortness of breath (1), pruritus, low back pain and chest pain (1), and blindness and grand mal seizure (1). One patient who had a history of blindness and grand mal seizure to Dexferrum (Iron Dextran) also reported pruritus on Day 1 of Venofer treatment and received oral Benadryl for treatment. This patient later reported severe diarrhea on Day 17 which was considered possibly related to study drug by the investigator and treatment with study drug was interrupted due to the diarrhea. This patient's pruritus on Day 1 responded to Benadryl treatment and could well represent an allergic reaction.

Among the 67 patients who did not report a history of allergy/intolerance to iron dextran, 11 patients had hypotension (definition was unclear), 3 had shortness of breath, and one had pruritus on adverse event records.

The sponsor did not provide the result regarding hypotension, as evidenced by a fall in systolic BP > 30 mmHg (one of criteria for acute anaphylactoid reaction) in the study report.

Clinical Laboratory Evaluations

The mean increases from baseline in mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) were observed at the final visit for all patients treated with iron sucrose injection [3.04 ± 0.389 fL for MCV (95% CI: 2.27, 3.82 fL), and 1.17 ± 0.160 pg for MCH (95% CI: 0.85, 1.49 pg)]. No statistically or clinically significant changes in any other hematology laboratory parameters were observed.

For serum chemistry, no statistically or clinically significant changes were observed from baseline to final visit in creatinine, alkaline phosphatase, total bilirubin, GGT, AST, ALT, LDH, sodium, potassium, chloride, calcium, glucose, and bicarbonate.

Statistically significant changes from baseline to final visit were observed for BUN/urea, albumin, and phosphorus. Mean BUN/urea and phosphorus levels significantly decreased while mean albumin levels significantly increased from baseline to final visit. These results are presented in the following table.

Table 17 Statistically Significant Changes From Baseline to Final Visit in Serum Chemistry Variables: Intent-to-Treat Patients

Variable	Iron Sucrose Injection (100 mg IV)	
	Intent-to-Treat Patients (N=77)	95% Confidence Interval
BUN/Urea (mg/dL)^a	N=63	
Baseline Mean	57.84 ± 2.535	
Final Visit Mean	52.19 ± 1.718	
Change at Final Visit		
Mean ± SEM	-5.65 ± 2.110	[-9.87, -1.43]
Median	-5.00	
Min, Max		
Albumin (g/dL)^b	N=63	
Baseline Mean	3.61 ± 0.043	
Final Visit Mean	3.70 ± 0.043	
Change at Final Visit		
Mean ± SEM	0.09 ± 0.031	[0.03, 0.15]
Median	0.10	
Min, Max		
Phosphorus (mg/dL)^c	N=55	
Baseline Mean	6.02 ± 0.291	
Final Visit Mean	5.43 ± 0.245	
Change at Final Visit		
Mean ± SEM	-0.60 ± 0.238	[-1.07, -0.12]
Median	-0.40	
Min, Max		

Extracted from Section 9, Table 6.2.

^a Lowest and highest limit of all normal ranges for BUN/urea: 4 - 30 mg/dL.

^b Lowest and highest limit of all normal ranges for albumin: 3.2 - 5.5 g/dL.

^c Lowest and highest limit of all normal ranges for phosphorus: 2.1 - 4.9 mg/dL.

Sponsor's table in NDA Vol. 14.2, pp. 72

It should be noted that while 1 patient had a positive pregnancy test and another had a borderline test at screening; the women were menopausal or postmenopausal and were not pregnant.

Vital Signs, Physical Findings and Other Observations Related to Safety

No clinically important differences in the observation period or in the treatment period were observed for changes in weight from pre- to postdialysis for all patients. On average, approximately 3 kg was lost from pre- to post dialysis.

Mean heart rate decreased slightly during dialysis over the observation period and the treatment period for all patients.

Mean systolic blood pressure generally decreased from predialysis to a low at 2 hours after the start of dialysis in the observation period or to a low at 2 hours after the start of study drug during the treatment period. No clinically meaningful differences between the observation and the treatment periods were seen for these changes. Slight decreases in mean diastolic blood pressure during dialysis were observed for all patients during both the treatment and observation periods.

No clinically important changes in temperature were observed during dialysis in either the treatment or the observation periods for all patients.

Forty-six of the 77 patients had abnormal but not clinically significant 12-lead electrocardiogram (12-lead ECG) results, 13 patients had clinically significant 12-lead ECG results, 16 had normal 12-lead ECG results at screening/prior to administration of study drug, and 2 patients did not have ECGs performed. End of treatment 12-lead ECGs were performed for 22 patients, all of which either were unchanged from the screening results or normalized (three patients).

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). No comparison can be made between LU98001 and historical control regarding to the safety.

7.1.1.5 Reviewer's Comments

LU98001 was a multicenter, open-label, historically controlled study in 101 chronic hemodialysis patients (77 patients treated with Venofer and 24 patients in matched cohort in historical control). The primary efficacy parameter was the change in hemoglobin level from baseline. The matched cohort in historical control was compatible with treatment population in terms of age, sex and baseline ferritin level but the populations were different in baseline hemoglobin, hematocrit, EPO dose, and transferrin saturation. To adjust these differences at baseline, the comparison in primary efficacy parameter between the two populations was made by ANOVA analysis including baseline hemoglobin, EPO dose and ferritin as covariates.

7.1.1.5.1 Efficacy Assessment

Study LU98001 demonstrated a significant increase in hemoglobin after Venofer treatment compared to the matched cohort in historical control at end-of-treatment ($p=0.0085$), 2 week follow-up ($p=0.0001$) and 5 week follow-up ($p=0.04$) in ANCOVA analysis with baseline hemoglobin, ferritin and EPO dose as covariates. Hematocrit was increased significantly from baseline in treatment group compared to matched cohort in historical control at end of treatment ($p=0.002$) and 2 week follow-up ($p=0.0003$) but not at 5 week follow-up ($p=0.13$) in the similar ANCOVA analysis. Ferritin ($p=0.0001$) and transferrin saturation ($p=0.0016$) were also increased significant at endpoint after Venofer treatment compared to matched cohort in historical population, which consistent with treatment effect of Venofer. The treatment effect for Venofer was approximately 1 g/dl increase in hemoglobin after 1 g Venofer injection given over 10 dialysis session over 4 weeks period. The maximum treatment effect for hemoglobin was seen at 2 week follow-up and the treatment effect remained at 5 week follow-up. The maximum treatment for ferritin was at the end-of treatment. The subgroup analysis did not show any age or sex effect on treatment.

The sponsor claims that 78% of ITT patients attained a hemoglobin level of ≥ 11.0 g/dl (NFK-DOQI guideline) during the LU98001 study. However, it should be noted that 21 (27.2%) patients already had baseline or screening hemoglobin level ≥ 11.0 g/dl and 27 (36.3%) patients had baseline hemoglobin level ranging from 10.0 to 10.9 g/dl.

7.1.1.5.2 Safety Assessment

In LU98001 study, 2 patients died following the end of Venofer treatment. The cause of the death was unclear but possible hypoglycemia or myocardial infarction for one patient who died at home and alone, and possible fasciomyonecrosis or coumadin necrosis for another patient. Fourteen of 77 patients reported 17 serious adverse events during the study and the most common serious adverse events were associated with application site reaction (3 patients). One patient discontinued the study drug permanently and 4 patients discontinued the study drug temporarily due to adverse events during the study. The most common adverse events were hypotension (17%), pain in extremities (10%), diarrhea (9%), application site reaction (9%), abdominal pain (8%) and accidental injury (6%). No patient reported life-threatening anaphylaxis reaction to study drug in the study. Of the 10 patients with a history of allergy/intolerance to iron dextran, one patient developed pruritus symptom and responded to Benadryl treatment. Among the remaining 67 patients who did not report a history of allergy/intolerance to iron dextran, 11 patients had hypotension (it was not predefined but was left to the investigator's discretion), 3 had shortness of breath (mild, required oxygen treatment, recovered) and 1 had pruritus (mild and no treatment given) in the study. No significant changes were observed in vital signs (except blood pressure mentioned early) and clinical laboratory evaluations in the study.

7.1.2 Trial 2: Study LU98002 (Vol. 1.28-1.29)

Study Investigators and Centers:

C. Charytan, MD, Nephrology Associate, Flushing, NY
M. Conen DO, FACP, Sharp Transplant Center, San Diego, CA
N. Levin, MD, Renal Research Institute, New York, NY
J. Roman, MD, Dallas Nephrology Associates, Dallas, TX

S. Zeig, MD. Clinical Studies Ltd, Fort Lauderdale, FL

Study Period: 12 January 1999 - 02 June 1999

7.1.2.1 Study Protocol

Title of the Study: An Open-Label Study of the Safety of Venofer [Iron Sucrose Injection] in Patients with Anaphylactoid Reactions to Iron Dextran.

7.1.2.1.1 Study Objective

The objective of this study was to determine whether iron sucrose could be safely administered to patients with dialysis-associated anemia who had demonstrated anaphylactoid reactions to iron dextran.

7.1.2.1.2 Study Design

This was a multicenter, single arm, open-label, baseline controlled study in patients with dialysis-associated anemia who had previously documented episode of anaphylaxis to iron dextran. Patients who enrolled in the study were administered a 100 mg dose of Venofer on day 1 and were monitored for 45 minutes for evidence of anaphylactoid reactions. Venofer was given either as a saline diluted slow infusion or as an undiluted slow injection within the first 60 minutes of dialysis. Blood pressure was recorded immediately before, and at 15 minute intervals after injection for the first 45 minutes, then hourly up to a total duration of 3 hours. If the patient tolerated the first dose of iron sucrose, 100 mg iron sucrose was administered at each dialysis session thereafter; up to 1000 mg iron was to be administered over 10 dialysis sessions (over 3-4 weeks). Patients were monitored for changes in blood pressure during each dialysis session and for adverse events throughout the study.

7.1.2.1.3 Study Population

At least 10 patients were to be enrolled and were to include two groups of patients:

- Group A: patients who had experienced mild anaphylactoid reactions to iron dextran i.e. urticaria.
- Group B: patients who had experienced severe anaphylaxis reactions to iron dextran i.e. bronchospasm, laryngeal edema, hypotension believed to be due to anaphylaxis, or angioedema, which may have required the use of bronchodilators or epinephrine.

Inclusion criteria were:

- Male or female patients over the age of 18
- Able to give informed consent
- Undergoing chronic hemodialysis 3 times weekly
- Hemoglobin concentration less than 11.0 g/dl
- Absence of infection, malignancy or surgery in the prior month
- Patients who have a documented history of anaphylaxis to parenteral iron dextran defined as any of the following:
 - Bronchospasm, as evidenced by dyspnea and wheezes
 - Laryngeal edema, as evidenced by stridor with or without edema
 - Hypotension, as evidenced by a fall in systolic BP > 30 mm Hg within 45 minutes of receiving iron

- Urticaria
- Angioedema

In addition, group B patients were to have transferrin saturation (TSAT) $\leq 20\%$ and serum ferritin ≤ 300 ng/mL.

Exclusion criteria were:

- Anticipated surgery or likely transplantation during the study
- Patients suffering from concomitant severe diseases of the liver [decompensated], cardiovascular system, severe psychiatric disorders or other which in the opinion of the investigator makes participation unacceptable
- Serum ferritin > 800 ng/ml or TSAT $> 50\%$
- Serious bacterial or viral infection or acute illness [e.g. hepatitis] unless completely resolved at least 4 weeks before inclusion
- HIV or Hepatitis B infection
- Asthma
- Patients who will probably need blood transfusion during the study
- Pregnancy or lactation
- Patients with causes of anemia other than iron deficiency (i.e. SLE, rheumatoid arthritis, and myeloma).

7.1.2.1.4 Study Drug

Venofer was supplied by Luitpold Pharmaceuticals, Inc. as 5 ml ampoules, containing 100 mg of iron as Fe[III]hydroxide sucrose complex and were administered through the dialysis line within 60 minutes from the start of the dialysis. All doses [1 ampoule/vial = 5 ml] were given intravenously either by slow infusion [diluted in 100 ml 0.9% NaCl and infused over 15-30 minutes] or by slow injection [undiluted, 20 mg/min injected over 5 minutes] with a hand held syringe or by infusion pump. For patients who had previously experienced a severe reaction to iron dextran, slow infusion was recommended. If adverse events occurred in patients who received Venofer by injection (undiluted), at the Investigator's discretion subsequent doses of Venofer could be diluted in 100 ml 0.9% NaCl, and administered by infusion over 15-30 minutes. Alternatively, Venofer could be diluted as described above and administered by infusion for all doses. A principal investigator or designee was to supervise administration of the study drug.

One ampule/vial Venofer was administered on each day of dialysis, which would be 3 times per week, for up to 10 dialysis sessions. A maximum of 3 ampoules/vials was administered per week. The total Venofer dose to be given during the treatment period could be up to 1000 mg. If a patient's serum ferritin exceeded 800 ng/ml or TSAT exceeded 50%, treatment with Venofer could be discontinued.

No additional iron preparations were allowed. Pre-medication with diphenhydramine, corticosteroids or similar drugs, was not allowed.

7.1.2.1.5 Study Plan

Each patient who qualified for inclusion according to medical history and data recorded in the medical record, was screened by medical history, physical examination, ECG, and clinical laboratory tests including hematology, iron study, chemistry, liver function test,

pregnancy test if applicable and HIV test if not done within 12 months. Consenting eligible patients were enrolled in the study. The study consisted of a pretreatment observation period and treatment period. The pretreatment period included three dialysis sessions prior to treatment Day 1; patients were monitored for clinically significant vital sign abnormalities and adverse events which may be associated with dialysis. This included adverse events occurring between dialysis sessions. Within thirty to sixty minutes after the start of each dialysis session, 100 mg of Venofer was completely administered. Patients visited the renal units 3 times per week according to individual hemodialysis sessions, and underwent routine hemodialysis as specified by the Dialysis Center. The sponsor's schedule of evaluations during the study is attached in Appendix 2.

Data collected at each dialysis session included date, starting time and completion time, body weight [pre- and post-dialysis], concomitant medication administered during dialysis session (e.g. rHuEPO), adverse events during dialysis session, dialyser new or re-used, blood loss, time of administration of the study drug. Clinical observations included blood pressure and heart rate recorded before dialysis session, before Venofer administration, every 15 minutes for the first 45 minutes and at 1, 2 and 3 hours after the start of administration of study drug. Oral temperature was recorded before the start of study drug administration and again at 15 minutes, 1, 2, and 3 hours after the start of administration of the study drug.

The laboratory assessments included hematological profile [hemoglobin, hematocrit, WBC, MCV, MCH, MCHC, reticulocyte count, platelets, differential count], iron studies [serum iron, serum ferritin, total iron binding capacity, percentage serum transferrin saturation], and clinical chemistry profile [sodium, potassium, chloride, BUN, creatinine, albumin, alkaline phosphatase, total bilirubin, GGT, AST, ALT, LDH, calcium, phosphorus, glucose, bicarbonate]. Blood samples for laboratory assessments were obtained according to the schedule of evaluation table.

A brief physical examination, comprising clinical assessment of skin, cardiovascular, pulmonary, abdominal and central nervous system, and reassessment of any previously abnormal findings was performed at each visit.

7.1.2.1.6 Efficacy Parameters

Hemoglobin, hematocrit, and iron indices were to be summarized using descriptive statistics. The sponsor did not indicate the change in hemoglobin or other measures as efficacy parameters.

7.1.2.1.7 Safety Assessment

The primary objective of the study was to determine whether intolerance occurs following the administration of Venofer in patients who have a known sensitivity to iron dextran. In particular, patients were evaluated for the development of anaphylaxis. Anaphylaxis was defined as development of any of the following within 45 minutes after administration of iron sucrose:

- Bronchospasm, as evidenced by dyspnea and wheezes
- Laryngeal edema, as evidenced by stridor with or without edema

- Hypotension, as evidenced by a fall in systolic BP > 30 mmHg
- Urticaria
- Angioedema

Adverse events were to be recorded throughout the study and graded as to severity (mild, moderate, and severe) and seriousness. Laboratory evaluations including clinical chemistry and physical examination, vital signs, weight were also evaluated for the safety assessment.

7.1.2.1.8 Statistical Methods

For safety analysis, results from the physical examinations, vital signs, hematological and clinical chemistry profiles, and adverse event recordings were summarized by descriptive statistics. All patients meeting the inclusion and exclusion criteria, and who received the study medication, were included in the safety analysis. The sponsor did not provide statistical methods for efficacy analysis.

7.1.2.2 Protocol Amendment: No amendment was made to the protocol.

7.1.2.3 Study Results

7.1.2.3.1 Disposition of Patients

A total of 23 hemodialysis patients were enrolled from 5 centers (16 patients in Group A and 7 patients in Group B). The following table shows the number of patients from each center:

Patient Enrollment by Center

Investigators	Study Centers	Number of Patients
C. Charytan, MD	Nephrology Associate, Flushing, NY	5 (1 Group A, 3 Group B)
M. Cohen, DO, FACP	Sharp Transplant Center, San Diego, CA	4 (Group A)
N. Levin, MD	Renal Research Institute, New York, NY	3 (2 Group A, 1 Group B)
J. Roman-LaTorre, MD	Dallas Nephrology Associates, Dallas, TX	7 (Group A)
S. Zeig, MD	Fort Lauderdale, FL	5 (2 Group A, 3 Group B)

Reviewer's table based on sponsor's data in NDA Vol. 1.29, pp. 2-3

All 23 patients received at least one 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%, Group A) discontinued the study on Day 22, after receiving 5 doses of iron sucrose, to obtain further care for progressive coronary artery disease. Patient disposition is summarized in the following table:

Patient Dispositions

Patient Dispositions	Group A	Group B	All Patients
	N (%)	N (%)	N (%)
Enrolled Patients	16(100%)	7(100%)	23(100%)
Completed Patients	15 (94%)	7 (100%)	22 (96%)
Discontinued Patients	1 (6%)	0	1 (4%)
Reasons for Discontinuation			
Needed further care for progressive coronary artery disease.	1 (6%)	0	1 (4%)

Reviewer's table based on sponsor's table in NDA Vol. 1.28, pp. 32

7.1.2.3.2 Protocol Deviations

A total of 21 patients (91.2%) had at least one protocol deviation in the study. The following table summarizes the protocol deviations:

Protocol Deviations

Deviations	Number of Patients
Violations of the Inclusion Criteria:	
Screening hemoglobin level \geq 11.0 g/dl	4
TSAT \geq 20% (Group B)	1
Questionable drug allergy/intolerance to iron dextran	5
Other Deviations:	
No day 1 hematology or serum iron indices data	7
Blood pressure reading > 5 minutes outside the scheduled time or missing	16
No end of treatment blood chemistries data	2
Dosing on nonconsecutive dialysis sessions	3
Received oral iron preparations during the study	3

Reviewer's table based on sponsor's tables in NDA Vol. 1.28, pp. 32-33

Review's Comments: Based on the sponsor's data (in NDA Vol. 1.29, pp. 26-28), the following table summarizes the symptoms and signs of reactions to iron dextran in Group A and Group B patients:

Symptoms and Signs of Reactions to Iron Dextran in 23 Enrolled Patients

Symptoms and Signs	Drug	Number of patients
Group A		
Urticaria	Iron Dextran	4
Itchy/back pain/felt hot	"IV Iron preparation"	1
Itchy/felt warm/erythematous	Iron Dextran	1
Itchy/pruritus	Dexferrum	1
Itchy	Dexferrum	1
Nausea/vomiting/upset stomach	Dexferrum	1
Dizziness/hypotension	Iron Dextran	1
Itching/SOB	Dexferrum	1
Chills/itching/rash to head	Iron Dextran	1
Itching and hives	Iron Dextran	1
Stomach cramp/flank pain	Iron Dextran	1
Severe back pain	Dexferrum	1
Rash/hypotension/SOB	Iron Dextran	1
Total		16
Group B		
Coughing/felt hot	Iron Dextran	1
SOB/nausea/chest pain/dizziness	Iron Dextran	1
SOB	Iron Dextran	1
SOB/ chest pain/ weakness/ chills/ back pain/ hypotension	Iron Dextran	1
Asthma/decreased blood pressure	Iron Dextran	1
Collapse	Infed	2
Total		7

Reviewer's table based on the sponsor's data in NDA Vol. 1.29, pp. 26-28.

According to the sponsor's inclusion criteria in the protocol, it appears that only 12 (52%) patients (with urticaria, hives, rash, itching/SOB, asthma/decreased blood pressure,

and collapse) satisfy the inclusion criteria. In hemodialysis patients, itching, SOB or hypotension alone without detailed clinical information regarding to the time of events, medical history, the treatment and outcome of each reaction is difficult to determine if those symptoms were due to anaphylactoid reactions. Other symptoms and signs were nonspecific (back pain and upset stomach); none of them satisfy the inclusion criteria based on available data. One patient received "IV iron preparation" without identifying the name of drug.

7.1.2.3.3 Data Sets Analyzed

The efficacy and safety analyses were based on the intent-to-treat population. A patient was included in the intent-to-treat population if the patient received at least one dose of study medication. All available data for the 23 patients (16 Group A, 7 Group B) were included in the efficacy and safety analyses. Safety and efficacy tables were presented by Group A and Group B separately and by the 2 groups combined.

7.1.2.3.4 Demographic and Baseline Characteristics

Of the 23 patients who received iron sucrose (100 mg iron/dialysis session), 13 (57%) were female and 10 (43%) were male. The mean age of all patients was 53 ± 17.6 years (range: 21-79 years). The ethnic origins of patients were 8 (35%) Caucasians, 8 (35%) blacks, 6 (26%) Hispanics and one (4%) Asian.

The following table summarizes patient demographics by sex for Group A and Group B patients and for all patients combined.

**APPEARS THIS WAY
ON ORIGINAL**

Table 6. Summary of Patient Demographics: Intent-to-Treat Patients

Variable	Iron Sucrose (100 mg IV) ^a					
	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 (yrs)						
Mean ± SD	50.3 ± 17.61	60.8 ± 16.99	50.0 ± 18.38	46.0 ± 18.99	50.2 ± 16.70	55.1 ± 18.55
Median	45.5	64.5	50.0	41.0	45.5	61.0
Min, Max	21, 75	31, 79	37, 63	27, 66	21, 75	27, 79
Ethnic Origin ^b						
Caucasian	3 (38%)	2 (25%)	1 (50%)	2 (40%)	4 (40%)	4 (31%)
Black	3 (38%)	3 (38%)	1 (50%)	1 (20%)	4 (40%)	4 (31%)
Asian	0	0	0	1 (20%)	0	1 (8%)
Hispanic	2 (25%)	3 (38%)	0	1 (20%)	2 (20%)	4 (31%)
Weight (kg)						
Mean ± SD	85.0 ± 16.78	63.5 ± 16.55	74.1 ± 12.25	58.9 ± 20.42	82.8 ± 16.03	61.7 ± 17.44
Median	86.8	64.7	74.1	55.4	83.9	58.9
Min, Max	65, 112	45, 94	65, 83	43, 93	65, 112	43, 94
Height (cm)						
Mean ± SD	173.2 ± 7.24	156.9 ± 3.55	173.4 ± 4.49	162.2 ± 7.06 ^c	173.2 ± 6.56	158.7 ± 5.34 ^d
Median	173.4	157.5	173.4	162.6	173.4	157.5
Min, Max	165, 188	152, 163	170, 177	155, 169	165, 188	152, 169

Extracted from Section 9, Tables 2.1 and 2.2.

SD: Standard Deviation; Min, Max: Minimum, maximum.

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

^b Percents were based on the number of patients in each subset.

^c Four patients were included in this analysis.

^d Twelve patients were included in this analysis.

Sponsor's table in NDA Vol. 1.28, pp. 35

Medical History/Concomitant Illness:

All patients had significant, ongoing medical conditions at entry. The majority of patients (>50%) had cardiovascular (most commonly hypertension) and endocrine/metabolic concurrent illnesses.

Physical Examination

Nineteen patients had at least one abnormal finding on physical examination at screening. The most common abnormal finding was systolic ejection murmur ≥II/VI grade (7/23 patients (30.4%).

Concomitant Medications/Treatment

All 23 patients received intravenous recombinant human erythropoietin (rHuEPO) 3 times/week prior to and during the entire study period. Six patients (26%) had their rHuEPO dose reduced an average of 35% (range: 10% - 80% of initial dose) during the treatment period and 2 patients (9%) had their rHuEPO dose increased during the treatment period.

Reviewer's Comments: Of 23 patients, 12 patients had received rHuEPO for less than 2 months, 7 patients for 2-4 months, and only 4 patients for more than 4 months (based on sponsor's data in NDA Vol. 1.29, pp. 38-41).

All 23 patients received at least 1 concomitant medication both during the observation period and during the treatment period. Among all 23 patients, the most common (250%) concomitant medications during the treatment period were other mineral (normal saline) supplements (78%), combinations of vitamins A and D (78%), antithrombotic agents (70%), calcium (70%), and agents acting on renin-angiotensin system (52%). During the treatment period, marked differences were seen between Group A and Group B patients in the reported use of some of the most common ($\geq 50\%$ of patients in either group) concomitant medications. These concomitant medications were as follows: antithrombotic agents (81% Group A, 43% Group B), calcium (75% Group A, 57% Group B), beta blocking agents (25% Group A, 57% Group B), other mineral supplements (88% Group A, 57% Group B), combinations of other vitamins (19% Group A, 71% Group B), selective calcium channel blocker with mainly vascular effects (25% Group A, 71% Group B), and vitamin B complex (50% Group A, 14% Group B).

Three (19%) Group A patients violated the protocol in that they received oral iron preparations during the entire study.

7.1.2.3.5 Efficacy Results

Efficacy results are summarized for the intent-to-treat population. If baseline data were missing, the screening data were used. If end-of-treatment data were missing, the patient was not included in the analysis.

Primary Efficacy Parameters:

Actual values and the change from baseline in hemoglobin, hematocrit, serum ferritin, and serum transferrin saturation were summarized by descriptive statistics (N, mean, standard error of the mean [SEM], median, minimum, and maximum) for each visit. A ninety-five percent (95%) confidence interval for the change from baseline in hemoglobin was calculated for the end of treatment visit.

An increase in the mean hemoglobin level was observed from baseline to end of treatment (95% confidence interval: 0.72-1.57 g/dl). When measured weekly, increases in mean hemoglobin levels were noticeable by Day 15 for all patients combined and for Group A patients, but not until Day 22 for Group B patients. The following table summarizes the mean change from baseline to the end of treatment in hemoglobin levels for all patients combined and for patients in Group A and B.

**APPEARS THIS WAY
ON ORIGINAL**

Table 7. Mean Change From Baseline in Hemoglobin: Intent-to-Treat Patients

Variable	Iron Sucrose (100 mg IV) ^a		
	Group A (N=16)	Group B (N=7)	All Treated Patients ^b (N=23)
Hemoglobin (g/dL)			
Baseline ^b			
N	15	7	22
Mean ± SEM	10.61 ± 0.225	9.90 ± 0.298	10.38 ± 0.190
Median	10.80	10.0	10.50
Min, Max			
End of Treatment (Day 24)			
N	15	7	22
Mean ± SEM	11.61 ± 0.282	11.34 ± 0.632	11.52 ± 0.270
Median	11.70	11.00	11.65
Min, Max			
Change at End of Treatment (Day 24)			
N	15	7	22
Mean ± SEM	1.00 ± 0.207	1.44 ± 0.473	1.14 ± 0.204 ^c
Median	1.00	1.50	1.15
Min, Max			

Extracted from Section 9, Tables 8.1 and 8.2.

SEM: Standard error of the mean; Min, Max: Minimum, maximum.

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

^b Baseline was the assessment taken just prior to the start of study drug administration (Day 1). If a patient's Day 1 value was missing, the screening value was used as baseline.

^c 95% Confidence interval = [0.72, 1.57]

Sponsor's table in NDA Vol. 1.28, pp. 37

Reviewer's comments: This was a baseline-controlled study. There were only two hemoglobin values (screening and baseline) available before study drug treatment. It was noted that there was some variation in hemoglobin levels between screening and baseline. There were 19 patients who had hemoglobin level measured at both screening and baseline and one of them had end-of-treatment hemoglobin value missing. The changes in hemoglobin at baseline compared to screening ranged from decreasing - g/dl to increasing + g/dl. A total of 14/18 (77.8%) patients had hemoglobin change within ±0.5 g/dl, 2 patients had hemoglobin increased more than 0.5 g/dl, and 2 patients had hemoglobin decreased more than 0.5 g/dl between screening and baseline. Based on this reviewer's analysis (Appendix 3), the mean increase in hemoglobin at the end-of-treatment from baseline was only 0.73 g/dl for patients with baseline hemoglobin variation ≤0.5 g/dl, which is much lower compared to the sponsor's result (1.04 g/dl) that included all patients.

Secondary Efficacy Parameters

Increases in mean hematocrit, serum ferritin and serum transferrin saturation (TSAT) levels were observed from baseline to the end of treatment. Increases in mean hematocrit levels were noticeable on Day 15 for all patients combined and for Group A patients and by Day 22 for Group B patients.

The following table summarizes the mean change from baseline to end of treatment in secondary efficacy variables.

Table 8. Mean Change From Baseline in Secondary Efficacy Parameters: Intent-to-Treat Patients

	Iron Sucrose (100 mg IV) ^a		
	Group A (N=16)	Group B (N=7)	All Treated Patients (N=23)
Hematocrit (%)			
Baseline ^b			
N	15	7	22
Mean ± SEM	33.47 ± 0.862	31.24 ± 1.026	32.76 ± 0.696
Median	33.50	30.80	33.35
Min, Max			
End of Treatment (Day 24)			
N	15	7	22
Mean ± SEM	36.79 ± 1.054	35.50 ± 2.045	36.38 ± 0.950
Median	36.50	37.00	36.75
Min, Max			
Change at End of Treatment (Day 24)			
N	15	7	22
Mean ± SEM	3.33 ± 0.546	4.26 ± 1.512	3.62 ± 0.593 ^c
Median	4.20	3.70	4.1
Min, Max			
Serum Ferritin (ng/mL)			
Baseline ^b			
N	14	7	21
Mean ± SEM	61.6 ± 19.18	28.9 ± 18.04	50.7 ± 14.28
Median	34.0	7.0	19.0
Min, Max			
End of Treatment (Day 24)			
N	14	7	21
Mean ± SEM	348.2 ± 46.54	254.6 ± 69.79	317.0 ± 39.03
Median	315.50	176.0	263.0
Min, Max			
Change at End of Treatment (Day 24)			
N	14	7	21
Mean ± SEM	286.6 ± 36.23	225.7 ± 55.58	266.3 ± 30.31 ^d
Median	278.5	154.0	234.0
Min, Max			
Serum Transferrin Saturation (%)			
Baseline ^b			
N	13	7	20
Mean ± SEM	17.23 ± 2.560	10.47 ± 1.879	14.87 ± 1.905
Median	15.00	9.00	12.3
Min, Max			
End of Treatment (Day 24)			
N	13	7	20
Mean ± SEM	23.85 ± 2.118	22.89 ± 3.315	23.51 ± 1.751
Median	25.0	20.0	22.9
Min, Max			
Change at End of Treatment (Day 24)			
N	13	7	20
Mean ± SEM	6.62 ± 2.093	12.41 ± 3.774	8.65 ± 1.943 ^e
Median	5.00	9.00	7.70
Min, Max			

Extracted from Section 9, Tables 9.1.1, 9.1.2, 9.2.1, 9.2.2, 9.3.1, and 9.3.2, and Appendix 10.1.9.

SEM: Standard error of the mean; Min, Max: Minimum, maximum.

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

^b Baseline was the assessment taken just prior to the start of study drug administration (Day 1). If a patient's Day 1 value was missing, then the screening value was used as baseline. For serum ferritin, Patient 0003000001 had no Day 1 value, therefore the screening value was used in this analysis.

^c 95% Confidence interval: [2.39, 4.86]

^d 95% Confidence interval: [203.1, 329.5]

^e 95% Confidence interval: [4.58, 12.71]

Sponsor's table in NDA Vol. 1.28, pp. 38-39

7.1.2.3.6 Safety Results

All 23 patients who received at least one dose of study medication were included in the safety analyses.

Extent of Exposure:

Thirteen of 16 patients in Group A and all 7 patients in Group B had 10 dialysis sessions and 10 doses of 100 mg iron as Venofer (1000 mg iron total dose). Two Group A patients received 9 doses of Venofer and one patient in Group A received 5 doses of Venofer before withdrawing from the study to obtain further care for progressive coronary artery disease. Nineteen patients received all Venofer doses undiluted over 5 minutes, 3 patients received all of their Venofer doses diluted in 100 mL 0.9% sodium chloride over approximately 30 minutes, and 1 patient received the first dose of iron as Venofer undiluted over 5 minutes and, because the patient reported pruritus during the first dose, all other doses were diluted and administered over 30 minutes without symptoms. The mean calculated total dose of iron sucrose as iron and the mean number of dialysis sessions are summarized in the following table.

Table 9. Total Dose and Duration of Study Drug: Intent-to-Treat Patients

	Iron Sucrose (100 mg IV) ^a		
	Group A (N=16)	Group B (N=7)	All Treated Patients (N=23)
Number of Dialysis Sessions			
Mean ± SD	9.6 ± 1.26	10.0 ± 0.00	9.7 ± 1.06
Median	10.0	10.0	10.0
Min, Max			
Calculated Total Dose Received (mg iron)			
Mean ± SD	956.3 ± 126.33	1000.0 ± 0.00	969.6 ± 106.32
Median	1000.0	1000.0	1000.0
Min, Max			

Extracted from Section 9, Table 4.

SD: Standard deviation; Min, Max: Minimum, maximum.

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

Sponsor's table in NDA Vol. 1.28, pp. 40

Adverse Events:

Ten of 23 patients (43%) reported at least one adverse event during the observation period and 18 of 23 patients (78%) reported at least one adverse event during the treatment period. In addition, 5 patients (22%) had adverse events which started in the observation period and which continued through to the treatment period. Only 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 treatment emergent. Only 2 adverse events (pruritus, taste perversion) were considered related to the use of iron sucrose by investigators.

Among all patients combined, the most common (>10%) adverse events during the observation period were hypertonia (muscle cramping, 26%) and hypotension (17%). Eight of 16 patients (50%) in Group A and 2 of 7 patients (29%) in Group B reported at

least one adverse event during the observation period. The most common (>10%) adverse events during the observation period were hypertonia (31%), hypotension (19%), headache (13%), pruritus (13%) in Group A and back pain, hypotension, and hypertonia (each 14%) in Group B.

Adverse events across the study are summarized by patient groups in the following table:

Table 10. All Adverse Events Across the Study by Body System: Intent-to-Treat Patients by Group

		Iron Sucrose (100 mg IV) ^a					
		Group A (N=16)			Group B (N=7)		
		Observation Period (N=16)	Continuing ^b (N=16)	Treatment Period (N=16)	Observation Period (N=7)	Continuing ^b (N=7)	Treatment Period (N=7)
Patients With at Least One Adverse Event		8 (50%)	3 (19%)	11 (69%)	2 (29%)	2 (29%)	7 (100%)
Body System	Preferred Term for Adverse Event						
Body as a Whole	Asthenia	0	0	3 (19%)	0	0	1 (14%)
	Headache	2 (13%)	0	4 (25%)	0	0	1 (14%)
	Infection	1 (6%)	0	1 (6%)	0	0	1 (14%)
	Injection Site Hemorrhage	0	0	0	0	0	1 (14%)
	Sepsis	0	0	0	0	0	1 (14%)
	Back Pain	0	0	0	1 (14%)	0	0
	Pain	1 (6%)	0	3 (19%)	0	0	0
	Gangrene	0	0	1 (6%)	0	0	0
	Face Edema	0	0	1 (6%)	0	0	0
Cardiovascular System	Hypotension	3 (19%)	0	6 (38%)	1 (14%)	0	4 (57%)
	Angina Pectoris	0	0	1 (6%)	0	0	0
Nervous System	Anxiety	0	0	0	0	0	1 (14%)
	Dizziness	0	0	3 (19%)	0	0	1 (14%)
	Hypertonia	5 (31%)	0	5 (31%)	1 (14%)	0	1 (14%)
	Hypertension	1 (6%)	2 (13%)	1 (6%)	0	0	0
Skin and Appendages	Application Site Reaction	0	1 (6%)	0	0	0	1 (14%)
	Pruritus	0	0	0	0	0	1 (14%)
	Swelling	0	0	0	0	0	1 (14%)
	Pruritus	2 (13%)	0	2 (13%)	0	1 (14%)	0
Respiratory System	Dyspnea	0	0	0	0	1 (14%)	2 (29%)
	Pharyngitis	0	0	1 (6%)	0	0	0
	Rhinitis	0	0	1 (6%)	0	0	0
Digestive System	Vomiting	0	0	1 (6%)	0	0	1 (14%)
	Diarrhea	0	0	1 (6%)	0	0	0
	Nausea	1 (6%)	1 (6%)	0	0	0	0
	Nausea and Vomiting	1 (6%)	0	1 (6%)	0	0	0
Musculoskeletal System	Leg Cramps	0	0	0	0	0	1 (14%)
	Myasthenia	0	0	1 (6%)	0	0	0
Special Senses	Taste	0	0	0	0	0	1 (14%)
	Purpura	1 (6%)	0	1 (6%)	0	0	0
Metabolic and Nutritional System	Hypervolemia	0	0	1 (6%)	0	0	0
	Peripheral Edema	0	0	0	0	1 (14%)	0

Extracted from Section 9, Table S.1.2.

Treatment Emergent Adverse Events

All adverse events 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 treatment emergent adverse events. Eighteen of 23 patients (78%) reported at least one treatment emergent adverse event. The most common (>10%) treatment emergent adverse events were hypotension (35%), headache, dizziness, and asthenia, (each 17%). The following table summarizes all treatment emergent adverse events by body system:

Table 11. All Treatment Emergent Adverse Events by Body System: Intent-to-Treat Patients

		Iron Sucrose (100 mg IV) ^a		
		Group A (N=16)	Group B (N=7)	All Treated Patients (N=23)
Patients With at Least One Adverse Event		11 (69%)	7 (100%)	18 (78%)
Body System	Preferred Term for Adverse Event			
Body as a Whole	Asthenia	3 (19%)	1 (14%)	4 (17%)
	Headache	3 (19%)	1 (14%)	4 (17%)
	Infection	1 (6%)	1 (14%)	2 (9%)
	Pain	2 (13%)	0	2 (9%)
	Face Edema	1 (6%)	0	1 (4%)
	Gangrene	1 (6%)	0	1 (4%)
	Injection Site Hemorrhage	0	1 (14%)	1 (4%)
	Sepsis	0	1 (14%)	1 (4%)
Cardiovascular System	Hypotension	4 (25%)	4 (57%)	8 (35%)
	Angina Pectoris	1 (6%)	0	1 (4%)
Nervous System	Dizziness	3 (19%)	1 (14%)	4 (17%)
	Anxiety	0	1 (14%)	1 (4%)
	Hypertonia	0	1 (14%)	1 (4%)
Skin and Appendages	Application Site Reaction	0	1 (14%)	1 (4%)
	Pruritus	1 (6%)	0	1 (4%)
	Rash	0	1 (14%)	1 (4%)
	Sweating	0	1 (14%)	1 (4%)
Respiratory System	Dyspnea	0	2 (29%)	2 (9%)
	Pharyngitis	1 (6%)	0	1 (4%)
	Rhinitis	1 (6%)	0	1 (4%)
Digestive System	Vomiting	1 (6%)	1 (14%)	2 (9%)
	Diarrhea	1 (6%)	0	1 (4%)
	Nausea and Vomiting	1 (6%)	0	1 (4%)
Special Senses	Taste Perversion	0	1 (14%)	1 (4%)
Musculoskeletal System	Leg Cramps	0	1 (14%)	1 (4%)
	Myalgia	1 (6%)	0	1 (4%)
Metabolic and Nutritional System	Hypervolemia	1 (6%)	0	1 (4%)

Extracted from Section 9, Tables 5.2.1 and 5.2.2.

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

Note: Patients were counted only once in each body system or preferred term. Percentages were based on the total number of patients in each subset.

Sponsor's table in NDA Vol. 128, pp. 43

Eleven of 16 patients (69%) in Group A and seven patients (100%) in Group B reported at least one treatment emergent adverse event. In each of the patient groups, the most common (>14%) treatment emergent adverse events were hypotension (25%), asthenia (19%), dizziness (19%), and headache (19%) in Group A patients and hypotension (57%) and dyspnea (29%) in Group B patients.

Hypotension was reported as an adverse event only in the observation period for 2 patients (1/16 Group A, 1/7 Group B), in both the observation and the treatment period for 2 patients (2/16 Group A) and only in the treatment period for 8 patients (4/16 Group A, 4/7 Group B). For the purposes of reporting adverse events, hypotension was not predefined but was left to the investigator's discretion. The sponsor indicated that there was a lack of consistency between investigators and even for individual investigators in which blood pressure changes of >30 mmHg they reported as adverse events. For 2 patients, hypotension in the treatment period was reported with a <30 mmHg drop in systolic blood pressure. All of the patients with hypotension reported as an adverse event were treated with saline for this event. None of these events were considered by the investigators to be related to study drug. It is of note that hypotension was reported as an adverse event for 5 of 39 (13%) dialysis/infusion sessions in 2/4 patients in whom the diluted drug was infused slowly over 30 minutes and in 19 of 174 (11%) dialysis/slow injection sessions in 9/19 patients in whom the undiluted drug was injected slowly over 5 minutes.

Treatment Emergent Adverse Events by Severity

The majority of treatment emergent adverse events for all patients were considered mild (14 patients, 61%) or moderate (1 patient, 4%). Three of 23 patients (13%) each had one treatment emergent adverse event considered severe, including 2/16 patients (13%) in Group A (gangrene and angina pectoris) and 1/7 patients (14%) in Group B (sepsis). All of the treatment emergent adverse events of hypotension were considered mild in severity.

Treatment Emergent Adverse Events by Causality

Two of the 23 patients (9%) had at least one adverse event that was considered to be related to study medication. One patient (6%) in Group A reported pruritus and 1 patient (14%) in Group B reported taste perversion (metallic taste) that were considered to be related to study medication. One patient who developed pruritus during administration received the first dose of iron sucrose undiluted over 5 minutes and, all other doses were diluted and administered over 30 minutes; no other symptoms of intolerance to iron sucrose were reported in this patient. None of the treatment emergent adverse events of hypotension (8 of 23 patients, 35%) were considered to be related to study medication.

Discontinuations Due to Adverse Events:

No patients were discontinued from this study due to an adverse event.

Serious Adverse Events:

Three serious adverse events were reported during the course of this study. One Group A patient (angina pectoris) and 1 Group B patient (sepsis) each had a serious adverse event during the treatment period and 1 Group A patient had a serious adverse event (gangrene) at follow-up. Patient 0001-000002 (only received 5 doses of study medication) in Group A entered the study with angina pectoris. The condition was considered serious on Day 1 and the patient was hospitalized. None of the serious adverse events were considered by the investigator to have a relationship to study medication. The following table summarizes all serious adverse events in this study.

Table 12. Serious Adverse Events: Intent-to-Treat Patients

Patient Number-Age/Gender/Group	Preferred Term	AE Start Day ^a /Period	AE Duration (days)	Relationship	Treatment and Outcome
US0001-000002-61/F/A	Angina Pectoris	1/T	4	None	Hospitalized for 4 days Recovered
US0003-000003-27/F/B	Sepsis	3/T	21	None	Vancomycin Tobramycin Gentamicin Recovered
US0004-000004-68/F/A	Gangrene	34/F	81	None	IV heparin Left femoral-popliteal by pass graft Amputation of toes 2, 3, 4, and 5 of the left foot Ciprofloxacin Recovered

Extracted from Listings 8.2 and 10.4 and adverse event report.

^a Days were calculated relative to the start of study medication, such that the first day of study medication was Day 1.

Note: T: Iron sucrose treatment period; and F: "follow-up"; after the Day 24 (end of treatment) visit.

Sponsor's table in NDA Vol. 1.28, pp. 45

Death:

No death was reported during the course of this study.

Anaphylactoid Reactions:

Patients who had bronchospasm, as evidenced by dyspnea and wheezes; laryngeal edema, as evidenced by stridor with or without edema; hypotension, as evidenced by a fall in systolic BP > 30 mmHg; urticaria; and/or angioedema within the first hour of administration of study drug that were considered by the investigator to have been related to study drug were to be considered to have had an acute anaphylactoid reaction to IV iron sucrose.

The sponsor indicated that no patient experienced bronchospasm, laryngeal edema, urticaria or angioedema as symptoms of an anaphylactoid reaction. However, 2 patients reported dyspnea (Group B patients), 1 reported pruritus (Group A patient), and 8 reported hypotension (4 Group A patients and 4 Group B patients) during the treatment. These events were considered by investigators to be mild and unrelated to study drug. The sponsor concluded that none of these events are signs of anaphylactoid reactions.

Hypotension was not predefined but was left to the investigator's discretion according to the sponsor. For 2 of these patients, hypotension was reported as an adverse event with a <30 mmHg drop in systolic blood pressure. All of these episodes of hypotension were considered by the investigator to be mild and unrelated to study drug, and these events were not considered by the investigators to be signs of anaphylactoid reactions. Of the 8 patients who had hypotension reported as an adverse event only in the treatment period, 2 patients had hypotension reported on Day 1.

Reviewer's Comments: It should be noted that one patient developed pruritus during administration of the first dose of iron sucrose. The event was considered by the investigator to be mild and probably related to study drug. Another patient developed facial rash in beard area 10 minutes after starting the 6th dose (Day 13) of Venofer injection. Two patients developed mild dyspnea during the study treatment period and one of them required oxygen treatment. There were 10 patients who experienced SBP drop of >30 mmHg within the first hour of study drug administration. Of these 10 patients, 6 patients had SBP drop of >30 mmHg occurring in at least one session during the observation period and 4 patients had SBP drop of >30 mmHg (3 patients in one dialysis session, 1 patient in 4 dialysis sessions) in the treatment period without SBP drop of >30 in previous observation period (Based on sponsor's data in NDA Vol. 1.29, pp. 64-174). These results suggests that some patients who had intolerance to iron dextran may also have intolerance to Venofer.

Clinical Laboratory Evaluations:

Statistically significant increases from baseline in mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) were observed at the final visit for all patients treated with iron sucrose [4.59±0.665 fL for MCV (95% CI: 3.21, 5.97 fL), and 1.40 ±0.255 pg for MCH (95% CI: 0.88, 1.93 pg)]. The mean changes in these variables were slightly larger for Group B than Group A patients. No statistically or clinically significant changes in any other hematology laboratory parameters were observed.

No statistically or clinically significant changes were observed from baseline to end-of-treatment in any serum chemistry parameter, including albumin, alkaline phosphatase, total bilirubin, GGT, AST, ALT, LDH, sodium, potassium, chloride, calcium, phosphorus, glucose, and bicarbonate.

Vital Signs:

No clinically important differences in the observation period and the treatment period were observed for changes in weight from pre- to postdialysis for all patients and for patients in Groups A and B. Mean heart rate decreased slightly during dialysis over the observation period and the treatment period for all patients and for patients in Group A and B. Mean systolic blood pressure decreased from predialysis to a low at 2 hours after the start of dialysis in the observation period or to a low at 2 hours after the start of study drug during the treatment period. Slight decreases in diastolic blood pressure during dialysis were observed for all patients during both the treatment and observation periods. Similar changes were seen for Group A and B patients. No clinically important changes in temperature were observed during dialysis in either the treatment or the observation periods for all patients, Group A patients or Group B patients.

ECG:

Ten of the 23 patients had abnormal but not clinically significant 12-lead electrocardiogram (12-lead ECG) results and 2 patients had clinically significant 12-lead ECG results at screening. End of treatment 12-lead ECGs were performed for 4 patients and all were unchanged from the screening results.

7.1.2.4 Reviewer's Comments

7.1.2.4.1 Efficacy Assessment

LU98002 showed a significant increase in hemoglobin from baseline after Venofer treatment ($p=0.0003$, calculated by this reviewer). Hematocrit, ferritin and transferrin saturation also increased significantly after Venofer treatment. The study results were consistent with the results in LU98001. The treatment effect was about 1 g/dl increase in hemoglobin after 1 g Venofer injection in 10 dialysis sessions over 4 weeks, which was similar to that seen in LU98001. This study was limited by only two baseline hemoglobin values available in this baseline-controlled study design. However, the overall results support Venofer use for hemodialysis associated iron deficiency anemia.

7.1.2.4.2 Safety Assessment

Study LU98002

The major deficiencies include following:

- 1) Only 12 patients (52%) of 23 enrolled patients satisfied the inclusion criteria according to the study protocol. The sponsor did not provide adequate information for other patients to be enrolled in the study (i.e. details of symptoms and signs, time of event, treatment and outcome).
- 2) Blood pressure reading >5 minutes outside the scheduled time or missing in 16 patients (69.5%).
- 3) Two patients showed anaphylactoid reactions (pruritus and facial rashes).

Overall, no patient died during the study and 3 patients experienced SAEs including angina pectoris, sepsis and gangrene, respectively. The most common treatment emergent adverse events were hypotension (35%), headache, dizziness, and asthenia (each 17%).

7.1.3 Trial 3: Study VIFOR/001 (Vol. 1.18-1.27)

Study Investigators and Centers:

R. van Zyl-Smit, MBChB, Grootte Schuur Hospital, Cape Town, South Africa
M.R. Moosa, MBChB, Tygerberg Hospital, Cape Town, South Africa
C.D. Potgieter, MBChB, HF Verwoerd Hospital, Pretoria, South Africa
H.G. Viljoen, MBChB, Garden City Clinic, Johannesburg, South Africa
S. Naicker, MBChB, Addington Hospital, Durban, South Africa

Study Period: 8/1994 – 10/1995.

7.1.3.1 Study Protocol

Title of the Study: A multicenter study to investigate the tolerance, safety and efficacy of intravenous iron sucrose in hemodialysis patients with anemia.

7.1.3.1.1 Study Objectives

The primary objective was to assess the tolerability and safety of intravenous iron sucrose therapy in patients with hemodialysis associated anemia. The secondary objective was to

assess the efficacy of intravenous iron sucrose therapy in correcting iron deficiency and hematological response in patients with hemodialysis associated anemia.

7.1.3.1.2 Study Design

This was a multicenter, single arm, open-label, baseline controlled study. The study consisted of a treatment period and a one-month observation period following the treatment. The treatment period for individual study subjects was dependent on the time needed to administer the total iron sucrose doses which were based on the baseline hemoglobin level and body mass.

7.1.3.1.3 Study Population

One-hundred patients with hemodialysis associated anemia from 4 centers (25 patients at each center) were to be enrolled in the study.

Inclusion criteria were:

- Male or female patient aged 18-75 years
- Undergoing chronic hemodialysis (2 to 3 per week)
- Iron deficiency anemia associated with a hemoglobin concentration ≤ 10 g/dl and a serum transferrin saturation $\leq 20\%$
- Clinically stable during the 4 weeks preceding the screening day
- Female patients who had to be sexually inactive or practicing reliable forms of contraception (where applicable)
- Informed consent

Exclusion criteria were:

- Clinical suspicion of iron overload
- Serum ferritin > 200 ng/ml
- Significant cardiac disease, decompensated liver disease, progressive chronic polyarthritis
- Serious bacterial or viral infection or acute illness e.g. hepatitis, unless completely resolved at least 4 weeks before inclusion
- Active peptic ulcer disease
- Known hypersensitivity to intravenous iron products
- HIV or hepatitis B positive
- Asthma
- Blood transfusion within 8 weeks of inclusion in the study, likely need for blood transfusion within 2 months of the start of the study,
- Anticipated surgery of any kind, temporary vascular access or inadequate vascular access
- Pregnancy or lactation
- Participation in any other therapeutic trial within the previous month,
- Use of parenteral iron preparations within 2 weeks before blood sampling for baseline (screening) hematological and iron studies

Withdrawal and replacement of patients:

Any patient who wished to withdraw from the study was allowed to do so at any time without the need to justify the decision. The investigators could withdraw a patient from the trial for the following reasons:

- Unacceptable adverse events, including concomitant diseases, whether or not related to the study medication.
- A serum ferritin value persistently above 1000 ng/ml, i.e. at 2 consecutive

measurements. In the event of a serum ferritin value above 1000 ng/ml, the serum ferritin had to be repeated at the start of the next hemodialysis session, and the patient was then withdrawn if the repeated value was > 1000 ng/ml.

- Renal transplant.
- Blood loss or other reasons necessitating blood transfusion.

All patients withdrawn from the study before completion of the treatment period (i.e. before they received the total Venofer dose) were to be replaced. Patients withdrawn from the study during the observation period, after having completed the treatment period, were not to be replaced.

7.1.3.1.4 Study Drug

Venofer as iron in Fe (III) oxide sucrose complex was manufactured and supplied by Vifor (international) Inc, Switzerland. The dosage form was 5 ml ampoule containing 100 mg Fe (III) in iron oxide sucrose complex, with sodium chloride. The study drug was administered into hemodialysis line one hour after the start of the dialysis session. The test dose was 2.5 ml containing 50 mg Fe (III) diluted in 50 ml 0.9% NaCl administered within 3-10 minutes. If no anaphylactoid reaction to the test dose was observed, the subsequent dose was 5 ml containing 100 mg Fe(III) diluted in 100ml 0.9 NaCl administered within 5-15 minutes and 2 to 3 times per week depending on individual hemodialysis sessions. The cumulative dose to be given during the treatment period was calculated individually according to the table below using baseline pre-dialysis hemoglobin level and pre-dialysis body mass. A maximum of 3 ampoules was to be administered per week.

Total Venofer dose (number of ampoules) to be administered during the treatment period

Pre-dialysis Body Mass (Kg)	Baseline Pre-dialysis Hemoglobin Level (g/dl)			
	<6	6.1-7.5	7.6-9.0	9.1-10.0
30-34	10	9	8	7
35-39	13	12	10	9
40-44	14	12	11	10
45-49	15	13	12	10
50-54	16	14	12	11
55-59	17	15	13	11
60-64	18	16	14	12
65-69	19	17	15	12
70-74	20	18	15	13
75-79	21	19	16	13
80-84	23	20	17	14
85-89	24	21	17	14
90-	25	22	18	15

Reviewer's table based on the sponsor's table in NDA Vol. 1.18, pp. 234

Any concomitant medication was to be recorded. No additional iron preparations were to be allowed.

7.1.3.1.5 Study Plan

Patients with history of chronic renal failure under dialysis treatment based on medical records were screened by medical history, physical examination, ECG if not done within 4 weeks, hematological tests (hemoglobin, hematocrit, MCV, MCHC, MCH, reticulocyte

count, erythrocytes, platelets, leukocytes and differential), clinical chemical tests (urea, creatinine, albumin, liver function tests, GGT, LDH), iron studies (serum ferritin, total iron binding capacity, serum transferrin saturation), pregnancy test if female in child-bearing age, HIV and hepatitis B serology test if not previously done. Screening was completed within two weeks before administration of the test dose of study drug to verify eligibility of subject and collect baseline data.

Eligible and consenting patients were given test dose of Venofer within 2 weeks of the screening period. If no anaphylactoid reaction was observed, 5 ml Venofer (1 ampoule, 100mg Fe (III)) in 100 ml 0.9% NaCl was administered during every subsequent hemodialysis session. Total Venofer dose for each subject was calculated according to the previous table.

Data collected and recorded on each dialysis session included date, starting time and completion time of dialysis, time of administration of study drug, body mass, concomitant medication administered during dialysis, adverse events during dialysis session, dialyser re-used or new. Clinical observations including blood pressure and heart rate were to be recorded before the start of the dialysis session, 1 hour after start of dialysis, at 15 minutes, 1, 2, and 3 hours after start of administration of study drug. Oral temperature was to be recorded at 15 minutes, 1 and 2 hours after start of administration of study drug. Adverse events between dialysis sessions were recorded. A physical examination, comprising clinical assessment of cardiovascular, pulmonary, abdominal and central nervous system functions, was to be performed and recorded monthly. The sponsor's study schedule is attached in Appendix 2.

Blood samples were obtained before the start of each dialysis session. Blood samples for hematology, iron studies and clinical chemistry were collected according to above study schedule.

Patients completed the treatment period once the total Venofer dose had been administered. The observation period was a one-month period immediately following the treatment period. At the end of the observation period, a physical examination was performed and a CRF was to be completed.

7.1.3.1.6 Efficacy Parameters

The sponsor indicated that efficacy was assessed through the hematological response including hemoglobin, MCV, MCH, MCHC and iron studies (serum ferritin, total iron binding capacity and serum transferrin saturation). The sponsor did not specify that the changes in hematological measures and iron studies were to be efficacy parameters.

7.1.3.1.7 Safety Assessment

Adverse events were recorded with time, duration, severity (mild, moderate, severe, serious), treatment required, dose adjustment, hospitalization, course, relationship to test drug (related, possible related, not related) and outcome. Any SAEs were to be reported within 24 hours by telephone to study monitor. Vital signs, physical examination and clinical chemical tests were included in the safety assessment.

7.1.3.1.8 Statistical Methods

A sample size of 100 patients was planned for the study. The sponsor did not provide the rationale for sample size estimation.

For efficacy analysis, the sponsor indicated that an intention-to-treat analysis was not to be performed in the study because the primary objective of the study was to assess tolerability and safety. Efficacy analysis included only patients who had no additional iron preparation, without EPO use or with EPO use at a constant dose from 1 month before and for the duration of the study, and no excessive blood loss in the duration of the study. Descriptive statistics included mean, standard deviation, geometric mean, geometric standard deviation, coefficient of variation, standard error of the mean, maximum, minimum and median value were to be given for each assessment. The Fe(III) dose-response relationship was to be determined. The sponsor did not specify statistical test to be used for efficacy analysis.

All patients who complied with the inclusion and exclusion criteria, and who had received the study medication were included in the safety analysis. Results from adverse events, physical examination, vital signs, clinical chemistry and hematological profiles were to be summarized by descriptive statistics.

7.1.3.2 Protocol Amendments

The original protocol was dated June 10, 1994. The protocol was amended on two separate occasions (1/17/1995, 3/13/1995). In protocol amendment No 1, the fifth study center in Addington Hospital, Durban, South African was added because the recruitment of participants in the planned four centers was slower than anticipated. A second monitor of study was also added. In protocol amendment 2, interim analysis for initial recruited 40 patients was added in order to speed eventual registration of product in South Africa.

7.1.3.3 Study Results

7.1.3.3.1 Disposition of Patients

A total of 132 subjects at 5 centers were enrolled in the study. The following table presents the number of patients from each center:

Study Centers	Number of Patients Enrolled	Number of Patients Included in Efficacy Analysis
Site #0001	41	37
Site #0002	9	7
Site #0003	3	1
Site #0004	63	48
Site #0005	16	12
Total	132	105

Reviewer's table based on the sponsor's data in NDA Vol. 12.1; Table 2.4J to 2.4n

Of the 132 enrolled patients, 131 patients received at least one treatment dose of study drug. One patient had blood transfusion three days prior to test dose administration and was withdrawn after test dose was administered; this patient was a 38 year-old coloured male who had a-baseline Hb of 8.7 g/dl and no adverse events reported. This patient was

excluded from both efficacy and safety analysis. Patient disposition is summarized in the table below:

Patient Disposition

Disposition	Number of Patients	%
Patients enrolled	132	100.0%
Patients treated	131	99.2%
Treatment period completed	109	82.6%
Observation period completed	98	74.2%
Reasons for withdrawn during treatment		
Renal transplant	12	9.1%
Lost-to-follow-up	2	1.5%
Blood transfusion	2	1.5%
Withdrawn for nephrectomy	2	1.5%
Protocol violation for exclusion	1	0.8%
Withdraw after SAEs	1	0.8%
Withdraw	2	1.5%
Reasons for withdrawn during observation after treatment completed		
Renal transplant	2	1.5%
Protocol violation	2	1.5%
Unknown reasons	7	5.3%
Patients included in safety analysis	131	99.2%
Patients included in efficacy analysis	105	79.5%
Patients excluded in efficacy analysis	26	19.7%
Reasons for exclusion for efficacy		
Protocol violation	6	4.5%
Renal transplant during the study	11	8.3%
Withdraw after serious AE	1	0.8%
Nephrectomy during the study	2	1.5%
Blood transfusion during the study	3	2.3%
Blood transfusion within 8 weeks prior to study	1	0.8%
Withdrawn	2	1.5%
Lost to follow-up	2	1.5%

Reviewer's table based on the sponsor's data in NDA Vol. 1.18, pp. 144-145 and 170-174; and Vol. 1.19, pp. 267-270.

One hundred and nine of the 132 patients completed the treatment; 98 patients completed the observation period. One hundred and thirty one patients who received at least one dose of study drug were included in the safety analysis and 105 patients were included in the efficacy analysis.

7.1.3.3.2 Protocol Deviations

The following table summarizes protocol deviations in the study:

**APPEARS THIS WAY
ON ORIGINAL**

Protocol Deviations

Protocol Deviations	Number of Patients
Violation of inclusion or exclusion criteria	
Age <18 years	1 (0.8%)
Baseline hemoglobin level >10 g/dl	2 (1.5%)
Screening serum ferritin >200 ng/dl	2 (1.5%)
Screening serum transferrin saturation >20%	2 (1.5%)
Blood transfusion within 8 weeks of inclusion in the study	1 (0.8%)
Consent form was signed after enrollment in the study	5 (3.8%)
Deviations	
Oral iron tablet continued in the study	2 (1.5%)
Serum ferritin levels >1000 ng/ml on two consecutive occasions during the treatment period but not withdrawn from the study	14 (10.6%)
Received one or two vials of study drug more than scheduled	8 (6.1%)
Received less than scheduled Venofer doses	20 (15.2%)
A range of 14-90 days between test dose day and the hematology and clinical chemistry screening day	24 (18.2%)
Blood transfusion during the study	3 (2.3%)
Pre-dialysis blood samples for some days were taken after the starting time of dialysis	15 (11.4%)
Observation was not completed	33 (25.0%)
Missing hemoglobin level in observation week 2	35 (26.5%)
Missing data for hemoglobin in post-study	2 (1.5%)
Missing baseline hemoglobin level	5 (3.8%)

Reviewer's table based on the sponsor's data in NDA Vol. 1.18, pp. 147-148, Vol. 18-23

7.1.3.3 Demographic and Baseline Characteristics

Of the 131 patients who received at least one treatment dose of Venofer, 69 (53%) were male and 62 (47%) were female. The mean age of 131 patients was 41.6 ±11.7 years (range 16-70 years). Of these 131 patients, 64 (49%) were coloured, 31 (24%) were black, 30 (23%) were white and 6 (4%) were Asian. The distribution of demographic features in the evaluable patients was similar to that in all patients who received at least one treatment dose of Venofer.

Demographic features in these two populations are summarized in the table below:

Demographic features of patients in study populations

		Patients who received at least one treatment dose of study drug			Evaluable Patients		
		Male (n=69) (52.7%)	Female (n=62) (47.3%)	Total (n=131)	Male (n=57) (54.3%)	Female (n=48) (45.7%)	Total (N=105)
Race	White	16(23.2%)	14(22.6%)	30(22.9%)	14(24.6%)	9(18.8%)	23(21.9%)
	Coloured	34(49.3%)	30(48.4%)	64(48.9%)	27(47.4%)	25(52.1%)	52(49.5%)
	Black	15(21.7%)	16(25.8%)	31(23.7%)	12(21.1%)	12(25.0%)	24(22.9%)
	Asian	4(5.8%)	2(3.2%)	6(4.6%)	4(7.0%)	2(4.2%)	6(5.7%)
Age (years)	Mean	44.0±12.0	38.9±10.8	41.6±11.7	45.5±11.9	39.5±10.7	42.7±11.7
	Range	19.5-70.3	16.7-66.9	16.7-70.3	19.5-70.3	16.7-66.9	16.7-70.3

Reviewer's table based on sponsor's data in NDA Vol. 1. 18, pp. 159-160 and sponsor's table 1-2 in NDA Vol. 1.19, pp. 7-19

Medical History

All patients who were included in the study suffered from chronic renal failure with associated anemia. Of these patients, 58 (44.3%) had previous renal transplants. The etiology of the renal failure was glomerulopathy (53.4%), vascular disease (15.3%), hypertension (8.4%), polycystic kidneys (6.9%), and other causes (16%).

The most common concomitant diseases were hypertension (84%), hyperparathyroidism (37%) and peritonitis (11%).

Concomitant Medication

Sixty-three patients (48%) had received ferrous sulfate before the start of the study. Two patients continued oral ferrous sulfate during the study. There were only 27 patients (21%) who received erythropoietin with the dosage range of 1000 to 4000 U, 2 to 3 times per week. Erythropoietin doses were kept constant for those patients during the duration of the study.

Reviewer's Comments: Of the 27 patients on EPO treatment, 5 patients had no starting date, 11 patients on EPO less than 4 months, and 11 patients more than 4 months (based on the sponsor's data in NDA Vol. 1.25, pp. 104-134; Vol. 1.26, pp. 1-34).

Other drugs that were frequently used in maintenance of these patients in the study were calcium carbonate and alfacalcidol (mainly for hyperphosphataemia), anti-hypertensive therapy, and vitamin supplements. Medications were most often introduced during the study were for musculoskeletal pain, infections and inadequate blood pressure control. During the dialysis sessions, 0.9% NaCl was used most frequently to control episodes of hypotension, muscle cramps and nausea.

7.1.3.3.4 Efficacy Results

Of the 131 patients who received at least one treatment dose of Venofer, 105 patients were included in the efficacy analysis and 26 patients were excluded from the efficacy analysis. For the 26 patients, the reasons for exclusion, study drug received and scheduled, and the hemoglobin level at baseline and last available level were listed in the following table:

APPEARS THIS WAY
ON ORIGINAL

Patients who were excluded from the efficacy analysis

Patient Number	Reasons for Patients Excluded for Efficacy Analysis	Venofer Dose Received/ Scheduled (ampoules)	Hemoglobin Level (g/dl)	
			Baseline	Last Available Value
13	Violated inclusion- Screening serum ferritin >200 ng/dl	12/17	4.5	5.1
18	Renal transplant during the treatment period	5/16	4.1	7.1
36	Withdrawn after serious adverse event	12/14	5.5	4.8
40	Violated inclusion- Screening serum transferrin saturation >20%	17/17	6.3	8.4
52	Protocol violator: Too many deviations and violations	13/13	6.5	11.7
53	Protocol violator: Too many deviations and violations	13/13	8.2	11.2
61	Renal transplant during the treatment period	13/18	7.5	8.9
64	Graft nephrectomy during the treatment period	5/17	6.3	5.4
66	GI bleeding and needed a transfusion during the treatment period	7/19	6.6	4.5
71	Renal transplant during the treatment period	1/23	7.1	7.8
106	Withdrew consent after 2 weeks- Patient claimed that study drug was making him drowsy	2/19	7.9	7.1
118	Fall in Hb necessitated transfusion during treatment period	5/16	6.6	4.6
119	Renal transplant during the treatment period	9/17	6.5	7.5
127	Required surgery and blood transfusion	3/19	4.4	5.7
132	Renal transplant during the treatment period	8/12	9.1	10.6
133	Renal transplant during the treatment period	1/13	9.9	11.4
135	Lost to follow-up after study day 10	10/23	5.3	5.7
145	Renal transplant during the treatment period	6/16	7.6	7.8
148	Never returned after study day 2	2/14	8.2	-
149	Renal transplant during the treatment period	10/15	7.0	8.7
158	Renal transplant during the treatment period	15/15	8.7	10.3
160	Renal transplant during the treatment period	5/17	7.8	9.2
161	Withdrew for elective nephrectomy	3/22	7.6	9.2
162	Renal transplant during the treatment period	11/16	8.7	8.4
203	Violated inclusion- Screening serum ferritin >200 ng/ml	16/16	7.7	7.2
204	Violated inclusion- Screening serum transferrin saturation > 20%	19/19	8.3	11.3

Reviewer's table based on sponsor's report and data in NDA Vol. 1.18, pp. 144-148; Vol. 1.19, pp. 267-270; and Vol. 1.22, pp. 164-167

Reviewer's Comments: The sponsor listed patient #52 and #53 as "protocol violator: too many deviations and violations" in the study report and did not specify the types of protocol violations. The type of violations could not be identified from the sponsor's available data. Patient #52 had the test dose of study drug 90 days prior to screening date and did not complete observation period. For patient #53, the baseline date of hematology was not same as the test dose date; blood samples were drawn after starting dialysis for some days; and patient did not complete observation period. However, the above protocol deviations do not satisfy criteria for excluding patients from efficacy analysis according to the protocol.

Efficacy results were assessed by comparing the baseline values with observation week 2 (2 weeks after the treatment had completed) or post-study values (one month after the treatment had completed). For hematological values and iron studies, the change from baseline to endpoint was analyzed using the analysis of variance, after logarithmic transformation of data. The mean ratio and 95% confidence interval of mean ratio were calculated.

If data were missing for baseline, the screening value was used. There were 5 patients who used screening hemoglobin value as baseline due to missing data at baseline. For

hematology and iron indices data, if data were missing for observation week 2, the last value obtained during the treatment period was used; missing data at post-study were replaced by the last available value for either the observation or treatment period. Of the 105 patients who were included in the efficacy analysis, 35 patients had missing data for hemoglobin level in observation week 2 and 2 patients had missing data for hemoglobin in post-study (based on the sponsor's data in NDA Vol. 1.22, pp.164-167).

The descriptive statistics of hematology and iron studies at baseline, observation week 2 and post study from all 131 patients who received at least one treatment dose of Venofer are summarized in the following table:

Hematology and iron studies in all patients who received at least one treatment dose of study drug (n = 131): Observation week 2 and post-study vs. baseline

Efficacy Measures	Baseline		Observation Week 2		Post Study	
	Mean±SD	Range	Mean±SD	Range	Mean±SD	Range
Hemoglobin (g/dl)	7.2±1.6	—	8.8±2.0	—	9.0±2.0	—
MCV (fL)	83.6±9.7	—	89.0±7.9	—	89.3±7.8	—
MCH (pg)	27.0±3.4	—	29.0±2.8	—	29.1±2.7	—
MCHC (g/dl)	32.1±1.7	—	32.4±1.8	—	32.5±1.6	—
Hematocrit (%)	22.4±4.8	—	27.1±6.3	—	27.7±6.4	—
Serum ferritin (ng/ml)	74.5±76.9	—	486±336	—	450±361	—
TIBC* (µmol/L)	54.9±13.8	—	44.3±10.9	—	43.7±12.9	—
Serum transferrin Saturation (%)	13.6±6.6	—	25.8±11.8	—	25.7±12.6	—

TIBC: total iron binding capacity

SD: standard deviation

Reviewer's table based on sponsor's Table 15 and Table 18 in NDA Vol. 1. 18, pp. 191 and 194.

For the 105 patients who were included in the efficacy analysis, the mean change of efficacy parameters from baseline to observation week 2 and post-study is summarized in the table on the next page.

The mean hemoglobin level increased significantly in observation week 2 and in post study compared to baseline with mean ratio of 128% (95% CI 123-133%, p<0.001). The mean levels of Hct, MCV and MCH were also increased significantly in observation week 2 and post-study compared to baseline. MCHC was unchanged from baseline to observation week 2 and post study based the mean ratio and 95% CI. Iron indices included serum ferritin and serum transferrin were increased significantly while total iron binding capacity decreased significantly in observation week 2 and post study compared to baseline (p<0.0001).

APPEARS THIS WAY
ON ORIGINAL

Mean ratio of hematology and iron studies of observation week 2 and post-study from baseline in evaluable patients (n = 105)

Efficacy Parameters	Baseline	Observation Week 2			Post-study		
	Mean±SD	Mean±SD	Mean Ratio* (95% C.I. #)	P-value	Mean±SD	Mean Ratio* (95% C.I. #)	P-value
Hemoglobin (g/dl)	7.3±1.6	9.2±1.8	128 (123-133)	≤0.0001	9.2±1.9	128 (123-133)	≤0.0001
MCV (fL)	83.1±9.3	89.6±7.2	108 (107-110)	≤0.0001	89.9±7.0	109 (107-110)	≤0.0001
MCH (pg)	26.9±3.4	29.2±2.5	109 (107-111)	≤0.0001	29.3±2.6	109 (107-111)	≤0.0001
MCHC (g/dl)	32.1±1.7	32.6±1.4	101 (100-103)	0.02	32.5±1.6	101 (99.9-102)	0.07
Hematocrit (%)	22.5±4.9	28.3±5.7	126 (121-131)	≤0.0001	28.6±6.1	127 (122-132)	≤0.0001
Serum ferritin (ng/ml)	68.4±66.8	455±275	1059 (861-1303)	≤0.0001	438±330	837 (680-1029)	≤0.0001
TIBC (μmol/L)	55.9±14.6	44.2±13.4	77.9 (74.2-81.7)	≤0.0001	43.6±13.8	77.9 (73.7-82.4)	≤0.0001
Serum transferrin saturation (%)	13.2±6.3	27.8±12.7	226 (201-254)	≤0.0001	27.7±12.6	219 (193-249)	≤0.0001

*: Estimate of observation week 2 or post-study over baseline means ratio from analysis of variance of log-transformed data.

#: 95% confidence interval for mean ratio after logarithmic transformation of data.

TIBC: total iron binding capacity; SD: standard deviation

Reviewer's table based on the sponsor's table 16, 17, 19 and 20 in NDA Vol. 1.18, pp. 192-193, 195-196.

Reviewer's Comments: This study was a baseline-controlled clinical trial. There were only two hemoglobin values available (screening and baseline) before the study drug treatment. There were 127 patients who had both screening and baseline hemoglobin levels available. It was noted that there were variations in hemoglobin level between screening and baseline. Nineteen (15%) patients had hemoglobin increased more than 0.5 g/dl between screening and baseline. This reviewer's analysis (Appendix 3) shows that the increase in hemoglobin level from baseline was higher in patients with baseline hemoglobin variation more than 0.5 g/dl compared to those with hemoglobin variation ≤0.5 g/dl. This suggests that baseline hemoglobin variation may have an effect on the study results.

7.1.3.3.5 Safety Results

A total of 131 subjects who received at least one treatment dose of Venofer were included in the safety analysis for treatment period.

Extent of Exposure:

The average doses of Venofer administered were 14.7±4.75 doses (100 mg/dose, scheduled 16.29±3.12 doses) with a range of 1-27 doses. A total of 111 patients (85%) completed the total treatment doses. Among those patients, 7 patients received one more dose and 1 patient received 2 more doses than scheduled (based on the sponsor's data in NDA Vol. 1.19, pp. 267-270)

Premature Withdrawals:

**APPEARS THIS WAY
ON ORIGINAL**

Twenty patients did not complete scheduled Venofer doses based on the sponsor's data. The reasons for withdrawal included screening serum ferritin >200 ng/ml (1), renal transplant in treatment period (10), withdrawn after SAE (graft rejection 1), nephrectomy surgery (2), withdrawn (1), patient's wish to withdraw (1), blood transfusion (2), lost-to-follow-up (2).

Adverse Events:

A total of 117 (89%) patients (111 (85%) during treatment period and 86 (79%) during the observation period) reported adverse events during the study. Hypotension (53%), cramps (44%), nausea (27%) headache (16%), vomiting (14%) and chest pain (10%) were the most frequently reported adverse events during the study, also during treatment period. Only 29 (22%) adverse events during treatment period and 5 (5%) events during observation period were judged to be possibly related to study drug by the treating physician.

The following table summarizes the adverse events reported in at least 2 patients or only in one patient but possibly related to the study drug:

Adverse events reported in at least two patients or in one patient only but possibly related to the study drug

Organ system and event	Total Events	Treatment period (n=131)		Observation period (n=109)	
		All events	Possibly or definitely related to study drug	All events	Possibly or definitely related to study drug
All	117 (89%)	111 (85%)	29 (22%)	86 (79%)	5 (5%)
Body as a whole					
Cramps	58 (44%)	48 (37%)	1 (1%)	33 (30%)	
Headache	21 (16%)	17 (13%)		5 (5%)	
Unwell	6 (5%)	2 (2%)		5 (5%)	
Fever/pyrexia	7 (5%)	4 (3%)			
Tiredness	4 (3%)	2 (2%)	1 (1%)	2 (2%)	
Flu symptoms	3 (2%)	3 (2%)			
Sleepiness	1 (1%)	1 (1%)	1 (1%)		
Cardiovascular system					
Hypotension	70 (53%)	61 (47%)	17 (13%)	49 (45%)	
Chest pain	13 (10%)	8 (6%)	2 (2%)	7 (6%)	
Hypertension	7 (5%)	6 (5%)	1 (1%)		
Vascular access problem	3 (2%)	1 (1%)		2 (2%)	1 (1%)
Angina pectoris	1 (1%)	1 (1%)			
Palpitation	2 (2%)			2 (2%)	
Tachycardia	2 (2%)	2 (2%)		2 (2%)	
AV fistula clot/clotting	2 (2%)	2 (2%)			
Hypervolemia	5 (4%)	4 (3%)		3 (3%)	
Digestive system					
Nausea	35 (27%)	31 (24%)	4 (3%)	18 (17%)	
Vomiting	18 (14%)	13 (10%)	2 (2%)	8 (7%)	
Raised liver enzymes	8 (6%)	5 (4%)	2 (2%)	4 (4%)	
Abdominal cramps	6 (5%)	5 (4%)	1 (1%)	3 (3%)	
Diarrhea	5 (4%)	5 (4%)			
Raised GGT	4 (3%)	3 (2%)		1 (1%)	
Hepatic congestion	3 (2%)	3 (2%)			
GI bleeding	2 (2%)	1 (1%)		1 (1%)	
Hemic and lymphatic system					
Drop in hemoglobin	6 (5%)	3 (2%)		3 (3%)	

Blood loss on dialysis	2 (2%)	2 (2%)			
Epistaxis	2 (2%)	2 (2%)			
Leukopenia	2 (2%)	1 (1%)		1 (1%)	
Neutropenia	2 (2%)	1 (1%)		1 (1%)	
Musculoskeletal system					
Musculoskeletal pain	8 (6%)	8 (6%)	1 (1%)		
Back pain	2 (2%)	2 (2%)			
Gout	2 (2%)	2 (2%)		1 (1%)	
Joint pain	2 (2%)	2 (2%)		1 (1%)	
Arthritis	1 (1%)			1 (1%)	1 (1%)
Tendosynovitis	1 (1%)			1 (1%)	1 (1%)
Nervous system					
Dizziness	9 (7%)	5 (4%)		4 (4%)	
Respiratory system					
Cough	5 (4%)	5 (4%)			
Pneumonia	5 (4%)	3 (2%)	2 (2%)	2 (2%)	1 (1%)
Dyspnea	3 (2%)	2 (2%)		1 (1%)	
Upper respiratory infection	3 (2%)			3 (3%)	
Severe pleural effusion	1 (1%)			1 (1%)	1 (1%)
Sore throat	2 (2%)	2 (2%)			
Chest infection	2 (2%)	2 (2%)			
Tuberculosis	1 (1%)			1 (1%)	1 (1%)
Sensory disorder					
Abscess ear/Purulent discharge ear	2 (2%)	2 (2%)	2 (2%)		
Skin and appendages					
Pruritus	4 (3%)	1 (1%)	1 (1%)	3 (3%)	
Itching	2 (2%)	1 (1%)		1 (1%)	
Rash	2 (2%)	1 (1%)	1 (1%)	1 (1%)	
Urinary system					
Dysuria	2 (2%)	2 (2%)		1 (1%)	
Graft rejection	2 (2%)	2 (2%)			
Urinary tract infection	2 (2%)	1 (1%)		1 (1%)	
Nephrectomy site problems	2 (2%)	2 (2%)			
Ferritin Level >1000 ng/dl	1 (1%)			1 (1%)	1 (1%)

Note 1: "raised liver enzymes" and "raised ALT" or "raised AST" listed as separated adverse events by the sponsor, which were combined as "raised liver enzymes" in above table by the reviewer.

Note 2: "Drop in hemoglobin", "Decreased Hb" and "Low Hb" listed as separated adverse events by the sponsor, which are combined as "drop in hemoglobin" in above table by the reviewer.

Note 3: "Rash" and "vascular rash" listed as separated adverse events by the sponsor, which are combined as "rash" in above table by the reviewer.

Note 4: "tight chest" and "chest pain" listed as separated adverse events by the sponsor, which are combined as "chest pain" in above table by the reviewer.

Reviewer's table based on the sponsor's data in NDA Vol. 1.18, pp. 149-196; Vol. 1.19, pp. 273-346

Death and Other Serious Adverse Events (SAEs):

Deaths

No death was reported from the sponsor's original study report. In the re-analysis report, the sponsor indicated that one patient died following rejection of a renal transplant after removal from the study (See 7.1.3.4.4 Re-analyzed Safety Results).

Other Serious Adverse Events (SAEs)

In the study report, 16 patients were reported as having a total of 21 SAEs during the study, including 15 SAEs during treatment period and 6 during observation period. The most common SAEs were pneumonia (5 patients), GI bleeding (2 patients) and graft rejection (2 patients). Six SAEs in 4 patients were considered by the investigator to be

related to study medication. These 6 SAEs were vascular access problem (1), pneumonia (2), tuberculosis (1), and pleural effusion (1). The following table summarizes all serious adverse events in this study based on the sponsor's study report:

Serious Adverse Events

Patient number	Sex	Age (yrs)	Adverse events	Study period	Relationship to study drug	Study medication change
4	M	30	Vascular access problem	Observation	Possible related	No
7	M	45	Pneumonia Tuberculosis Pleural effusion	Treatment	Missing Possible related	No
12	M	38	Hypoglycemia	Observation	Not related	No
14	F	25	Salpingo-oophoritis	Treatment	Not related	No
15	M	27	Pneumonia	Treatment	Possible related	No
20	M	38	Pneumonia	Observation	Possible related	No
21	M	39	Uveitis	Treatment	Not related	No
31	M	53	GI bleeding/Hypotension	Observation	Not related	No
36	F	23	Graft rejection	Treatment	Not related	Discontinued
62	F	41	Hernia repair	Treatment	Not related	No
64	M	26	Graft rejection	Treatment	Not related	Discontinued
66	M	43	GI bleeding	Treatment	Not related	Discontinued
118	F	36	Hemiparesis	Treatment	Not related	No
131	M	38	Dyspnea/Fever/Pneumonia	Treatment	Not related	No
144	F	45	Endophthalmitis	Treatment	Not related	No
203	M	62	Pneumonia	Observation	Not related	No

Reviewer's table based on the sponsor's data in NDA Vol. 1.18, pp. 151, 149-196; Vol. 1.19 pp. 273-346

Review's Comment: It was noted that 4 patients were hospitalized due to an adverse event but not listed as a serious adverse event by the sponsor in the study report. These SAEs were chest pain (2 patients), renal transplant (1 patient), and nephrectomy site problem (1). See table below:

Patients who were hospitalized but not listed as serious adverse event by the sponsor

Patient number	Sex	Age (yrs)	Adverse events	Study period	Relationship to study drug	Study medication change
16	M	57	Chest pain	Treatment	Not related	No
105	M	39	Chest pain, cramps	Treatment	Not related	No
119	F	25	Renal transplant	Treatment	Not related	No
127	F	40	Nephrectomy site problem	Treatment	Not related	Discontinued

Reviewer's table based on the sponsor's data in NDA Vol. 1.18, pp. 149-196; Vol. 1.19, pp. 273-346

Discontinuations and Decrease of Study Drug due to Adverse Events:

Eight patients discontinued study drug and 8 patients decreased study drug due to an adverse event in the study based the sponsor's data. Graft rejection (2 patients) was the most common event in patients who discontinued study drug and hypotension (4 patients) was the most common event in patients who decreased study drug. See following table:

APPEARS THIS WAY
ON ORIGINAL