

transferrin saturation were also significantly higher in Venofer group than in oral iron group ($p < 0.05$). Randomization was unclear in this study; it was mentioned in the overall study design and plan section only in the study report dated 1/27/99; it was not mentioned in any other place in the study report, nor in the original study publication dated 10/29/1997. The duration of prior EPO use was not provided. However, the overall study results supported the findings in pivotal trials. No adverse event was recorded for the 12-week study.

7.2.4 Trial 4: Study Schaefer (Vol. 1.31-1.33)

7.2.4.1 Study Protocol

Title of the Study: "A Single-Center, Open, Randomized, Controlled Study on Intravenous Iron Supplementation in Stable Renal Patients Treated with Erythropoietin".

Study Investigators: Med U. Bahner, MD, Kuratorium für Dialyse und, Würzburg, Germany.

Study Objectives: To compare the efficacy and safety of Venofer and Ferrlecit with respect to hemoglobin response, iron status and EPO dosage requirements in stable renal patients treated over six months.

Study Design: This was to be a single center, open-label, nonrandomized, concurrent treatment controlled study.

Study Population: Inclusion criteria were patients on regular hemodialysis (stable for at least three months), on EPO for at least four months and dose unchanged for two months, hemoglobin between 9 and 12 g/dl on three successive occasions in the past two months and Hb variability < 1.5 g/dl on these three successive occasions, serum ferritin 100 - 600 $\mu\text{g/l}$, normal serum B₁₂ and red cell folate levels, no other cause for anemia (SLE, rheumatoid arthritis, myeloma, etc.), absence of infection, malignancy or surgery in the past three months, serum C-reactive protein < 20 mg/l, no blood transfusions in the past three months.

Exclusion criteria were severe diseases of the liver (decompensated), cardiovascular system, severe psychiatric disorders or other disorder which in the opinion of the investigator makes participation unacceptable, clinical suspicion of iron overload, serum ferritin < 100 $\mu\text{g/l}$ or > 600 $\mu\text{g/l}$, serious bacterial or viral infection or acute illness e.g. hepatitis, unless completely resolved at least four weeks before inclusion, serum c-reactive protein > 20 mg/l, active peptic ulcer disease, known hypersensitivity to intravenous iron products, HIV or hepatitis B-positive patients, asthma, progressive chronic polyarthritis, blood transfusion within 12 weeks of inclusion in the study patients who will probably need blood transfusion within two weeks from the initiation of the study, anticipated surgery of any kind, pregnancy or lactation, insufficient contraception in women of childbearing age, use of parenteral iron preparations within two weeks before blood sampling for baseline (screening) special investigations, participation in any

other therapeutic trial within the previous month, or administration of any drug with a well-defined potential for toxicity in a major organ or organ system within the previous three months.

Study Drug: For patient assignment, the investigators decided to give Venofer to all even patient numbers (Group I) and to give Ferrlecit to all uneven patient numbers (Group II).

Group I: iron (III)-hydroxide sucrose complex (12.5 ml of Venofer) 250 mg was administered monthly. Iron (III)-hydroxide sucrose complex 250 mg was diluted in 100 ml normal saline, 10 ml (25 mg Fe(III)) are given within 15 minutes as test dose. In 15 minutes later, the remaining volume of the solution was infused within 45-60 minutes while dialysis was performed.

Group II: iron (III) sodium gluconate complex 62.5 mg (5 ml Ferrlecit) was administered weekly within 5 minutes while dialysis is performed.

Iron treatment was to be stopped if hemoglobin >12.5 g/dl or serum ferritin > 1000 µg/L, or if the preparation was not tolerated, if adverse events arose or if patient developed a severe bacterial infection or hepatitis. If hemoglobin increased by more than 20 % of baseline or to a value of >14 g/dl, EPO dose was decreased by 50 %. EPO dose was doubled if hemoglobin dropped >2 g/dl from four weeks before. No additional iron preparations were allowed.

Study Plans:

The study schedule is shown in the sponsor's study flow chart below:

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Flow chart

	Treatment period											
	Initial Screening	Week										
		-4	-2	0	2	4	8	12	16	20	24	
Informed consent	X											
Medical history	X											
Medication history	X											
Demographic / anthropometric data	X											
Physical examination	X											
Update physical examination		X	X	X	X	X	X					X
Update concomitant medication		X	X	X	X	X	X					X
Haemoglobin	X	X	X	X	X	X	X					X
Haematocrit	X	X	X	X	X	X	X					X
RBC	X	X	X	X	X	X	X					X
MCH	X	X	X	X	X	X	X					X
MCHC	X	X	X	X	X	X	X					X
MCV	X	X	X	X	X	X	X					X
% hypochromic RBCs		X		X		X	X					X
WBC + diff. count	X	X	X	X	X	X	X					X
Platelets	X	X	X	X	X	X	X					X
Reticulocytes	X	X		X		X	X					X
Serum transferrin / % saturation	X	X	X	X	X	X	X					X
Serum ferritin	X	X	X	X	X	X	X					X
Serum iron	X	X		X		X	X					X
Liver transaminases	X	X		X		X	X					X
CRP	X	X		X		X	X					X
Vitamin B12	X											
Serum folate	X											
rHuEPO dose	X	will be recorded under 'concomitant medication' in cases of dosage changes										
Adverse events		X	X	X	X	X	X					X

Sponsor's chart in NDA Vol. 1.31, pp. 217

Efficacy Parameters: Hemoglobin response, serum ferritin and erythropoietin dosage requirement over 6 months.

Safety Assessment:

Adverse events were classified as mild, moderate, severe and serious. Any serious adverse events were to be reported within 24 hours to the sponsor. The telephone notification was to be followed by a written report within 3 days of such an event.

Statistical Methods: Per-protocol population (PP) and intention-to-treat-population (ITT) were to be used for the primary parameter analysis. Per-protocol population excluded patients who violated protocol and who withdrew due to adverse event(s) related to study medications. A sample size of 100 hemodialysis patients was planned. The sponsor did not provide a rationale for the sample size estimation.

Descriptive statistics included median, mean and standard deviation for the pre-treatment and post-treatment values, as well as the pre-post differences. The geometric mean and the range were to be used when the variable follow the normal distribution after logarithmic transformation. Pre-post changes were to be given as ratios or percent changes. Clinical laboratory parameters were to be analyzed in a descriptive manner by marking all individual values outside the corresponding normal ranges. The independent t-test, at the 5%-level, two-sided was used to compare between the two formulations with regard to the primary and secondary parameters. The frequencies of adverse events were analyzed by the Chi-square test.

Protocol Amendment:

The protocol was amended on August 31, 1998. The following changes were made:

- Mrs. H. Bettger was added as an investigator
- Inclusion criteria #3 (EPO treatment dose unchanged for two months) was deleted.
- Inclusion criteria #7 (normal serum B12 and red cell folate levels) changed to "Vitamin B12 >200 pg/ml and RBC folic acid >2 ng/ml".
- Body temperature (as part of the physical examination) was not to be measured during the visits
- The pregnancy test in female patients was not to be performed.
- Change of the CRF: data on concomitant medication taken during the past three months were not to be entered since it corresponds to the concomitant medication at screening.
- Treatment assignment was not to be randomized.

7.2.4.2 Study Results

Disposition of Patients:

A total of 59 patients participated in the study. The disposition of patients is summarized in the table below:

Disposition	Venofer	Ferlecit	Total
Patients enrolled	29	30	59
Patients treated	27	28	55
Patient completed	14	19	33
Patients withdrawn	13	9	23
Reasons for withdrawn			
Consent withdrawn	1	0	1
Adverse event	4	3	7
Hemoglobin >12.5 g/dl	6	2	8
Ferritin >1000 ng/mL	2	1	3
Blood transfusion		1	1
Change of dialysis center	0	2	2

Reviewer's table based on the sponsor's data in NDA Vol. 1.31, pp. 233-234, 262-263

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ITT and PP populations are shown in the following table:

ITT and PP populations

	Venofer	Ferrlecit
Patients enrolled	29	30
ITT analysis	27	28
PP analysis	15	13
Reasons for exclusion from PP analysis		
Violation of inclusion criteria	8	10
Violation of exclusion criteria	1	1
Blood transfusion		1
Withdrawn	3	3

Reviewer's table based on the sponsor's data in NDA Vol. 1.31, pp. 233

Four patients were excluded from the safety population. Two patients were excluded because they had received no study medication and two because they did not have post-baseline safety data.

Protocol Deviations:

A total of 22 (37.2%) patients enrolled in the study violated inclusion/exclusion criteria (10 in Venofer group and 12 in Ferrlecit group. Nine patients had protocol deviations during the study (6 in Venofer group and 3 in Ferrlecit group).

The following table summarizes the types of protocol deviations:

Protocol Deviations

	Venofer	Ferrlecit
Hemoglobin not between 9-12 g/dl	3	4
Vitamin B12 > 180 pg/ml	2	1
serum c-reactive protein >20 mg/L	1	2
Other causes of anemia	1	2
Ferritin >600 µg/L	2	2
Blood transfusion within 12 weeks	1	
Malignancy		1
Iron was not stopped when hemoglobin >12.5 g/dl	4	2
Iron was not stopped when ferritin >1000 µg/L	2	
No blood sample collection in three times		1
Total patients	16	15

Reviewer's table based on the sponsor's data in NDA Vol. 1.31, pp. 233, 265-266

Demographic and Baseline Characteristics:

The demographic characteristics of the ITT and PP populations are summarized in the following tables:

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Demographic details - ITT/Safety populations

Demographic characteristic		Venofer® (n = 27)	Ferriect® (n = 28)	p-value
Sex	Male	10 (37.0%)	15 (53.6%)	0.2230*
	Female	17 (63.0%)	13 (46.4%)	
Race	White (Caucasian)	27 (100.0%)	28 (100.0%)	
Age (years)	Mean	57.2	60.9	0.3724**
	Median	59.0	66.0	
	Range	33 - 86	27 - 84	

* Mantel-Haenszel test

** t-test

Sponsor's table in NDA Vol. 1.31, pp. 238

Demographic details - PP population

Demographic characteristic		Venofer® (n = 15)	Ferriect® (n = 13)	p-value
Sex	Male	6 (40.0%)	9 (69.2%)	0.1290*
	Female	9 (60.0%)	4 (30.8%)	
Race	White (Caucasian)	15 (100.0%)	13 (100.0%)	
Age (years)	Mean	57.2	58.9	0.7628**
	Median	59.0	62.0	
	Range	33 - 86	27 - 75	

* Mantel-Haenszel test

** t-test

Sponsor's table in NDA Vol. 1.31, pp. 239

No significant differences were noted in demographic data between the two groups.

The most frequent concomitant diseases were hypertension (40 patients [72.7%]), type II diabetes mellitus (20 patients [36.4%]), ischemic heart disease (12 patients [21.8%]), and congestive heart failure (9 patients [16.4%]).

The frequent concomitant medications before the study were antianemic preparations (iron prep. and rHuEPO) (100%), vitamins (98.2%), mineral supplements (83.6%), antacids (80.0%), antithrombotic agents (63.6%), and analgesics (60.0%). The frequent concomitant medications during the study were rHuEPO (89.1%), vitamins (70.9%), antibacterials (50.9%), antacids (25.5%), mineral supplements (25.5%), cough and cold preparations (23.6%), drugs used for diabetes (23.6%), calcium channel blockers (16.4%), analgesics (14.5%), antihypertensives (12.7%), antithrombotic agents (12.7%), antipsoriatics (10.9%), ophthalmologicals (10.9%), and lipid reducing agents (10.9%).

Efficacy Results:

The mean hemoglobin changes in the two group at end of treatment (24 weeks) from baseline for ITT and PP populations are summarized in the table below:

Summary of mean haemoglobin [g/dL]

Treatment group	ITT population			-PP population		
	Baseline ^a	Endpoint ^b	Change ^{**}	Baseline ^a	Endpoint ^b	Change ^{**}
Venofer [®]	11.34	11.43	0.08	11.55	11.49	-0.07
Ferlecit [®]	11.33	11.42	0.09	11.11	11.45	0.35
Comparison between treatment groups (Venofer [®] - Ferlecit [®])						
Mean difference [Ⓞ]	-0.004			-0.09		
95% Confidence interval [*]	(-0.67; 0.66)			(-1.21; 1.02)		
p-value [*]	0.9899			0.8644		

- ^a Mean value at Week 0
- ^b Mean value at endpoint (obtained by means of last observation carried forward)
- ^{**} Endpoint - baseline
- [Ⓞ] Estimate of the mean difference between treatments at endpoint from analysis of covariance (with baseline as covariate)
- ^{*} 95% Confidence interval for the mean difference between treatments and the corresponding p-value from the analysis of covariance.

- Sponsor's table in NDA Vol. 1.31, pp. 242

There was no significant difference in mean hemoglobin between end of treatment and baseline in both Venofer and Ferlecit groups for either ITT or PP population. Also, there was no significant difference in mean hemoglobin between Venofer and Ferlecit groups at the end-of-treatment for either ITT (p=0.99) or PP population (p=0.86).

The following table summarizes the change in serum ferritin:

Summary of mean serum ferritin [ng/mL]

Treatment group	ITT population			PP population		
	Baseline ^a	Endpoint ^b	Change ^{**}	Baseline ^a	Endpoint ^b	Change ^{**}
Venofer [®]	412.5	650.1	237.7	406.0	661.7	255.7
Ferlecit [®]	369.1	650.2	281.1	412.7	691.2	278.5
Comparison between treatment groups (Venofer [®] - Ferlecit [®])						
Mean difference [Ⓞ]	-33.87			-25.02		
95% Confidence interval [*]	(-157.71; 89.97)			(-216.63; 166.60)		
p-value [*]	0.5854			0.7902		

- ^a Mean value at Week 0
- ^b Mean value at endpoint (obtained by means of last observation carried forward)
- ^{**} Endpoint - baseline
- [Ⓞ] Estimate of the mean difference between treatments at endpoint from analysis of covariance (with baseline as covariate)
- ^{*} 95% Confidence interval for the mean difference between treatments and the corresponding p-value from the analysis of covariance.

Sponsor's table in NDA Vol. 1.31, pp. 243

Increases in serum ferritin from baseline were observed in both treatment groups, but no significant difference was observed at endpoint between the two treatment groups.

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The following table summarizes the change of erythropoietin dosage requirements:

Summary of mean erythropoietin dosage requirements [U/kg/week]

Treatment group	ITT population			PP population		
	Baseline ^a	Endpoint ^b	Change ^c	Baseline ^a	Endpoint ^b	Change ^c
Venofer [®]	85.96	79.97	-6.00	85.35	86.20	0.85
Ferrlecit [®]	85.92	85.95	0.02	92.51	89.42	-3.09
Comparison between treatment groups (Venofer [®] - Ferrlecit [®])						
Mean difference ^d	-6.01			2.93		
95% Confidence interval ^e	(-25.82 ; 13.80)			(-21.21 ; 27.08)		
p-value ^f	0.5455			0.8045		

- ^a Mean value at Week 0 - 2
- ^b Mean value at endpoint (obtained by means of last observation carried forward)
- ^c Endpoint - baseline
- ^d Estimate of the mean difference between treatments at endpoint from analysis of covariance (with baseline as covariate)
- ^e 95% Confidence interval for the mean difference between treatments and the corresponding p-value from the analysis of covariance.

Sponsor's table in NDA Vol. 1.31, pp. 244

No significant difference was observed between the two treatment groups for the erythropoietin dosage requirements given over a period of 6 months.

Safety Assessment:

Fifty-five patients (Venofer 27 patients and Ferrlecit 28 patients) were included in the safety analysis. Two of the four patients who were excluded received no study medication while the other two patients received study medication but had no post-baseline safety data.

Adverse Events:

Thirteen patients (48.1%) in the Venofer group reported 21 adverse events, while 11 (39.3%) patients in the Ferrlecit group reported 22 adverse events. All the adverse events reported in both treatment groups were not related to study medication by the investigator.

The common adverse events in the two groups are summarized in the table below:

Adverse events in more than 2% of the total number of patients

Body System/ Costart term	Venofer [®]			Ferrlecit [®]		
	n	(m)	%	n	(m)	%
<i>Body as a whole</i>						
Flu syndrome	7	(7)	25.9	5	(5)	17.9
Infection	1	(2)	3.7	1	(1)	3.6
<i>Endocrine system</i>						
Surgery	2	(3)	7.4	0	(0)	0.0
<i>Hemic and lymphatic system</i>						
Hypochromic anaemia#	1	(1)	3.7	3	(3)	10.7
<i>Respiratory system</i>						
Pneumonia	1	(1)	3.7	2	(3)	7.1
Sinusitis	1	(1)	3.7	1	(1)	3.6
<i>Skin and appendages</i>						
Skin ulcer	2	(2)	7.4	0	(0)	0.0

Hypochromic anaemia (Costart term) [or drop in haemoglobin (Investigator's term)]

Sponsor's table in NDA Vol. 1.31, pp. 249

There were slightly more patients in the Venofer treatment group than in the Ferrlecit group with adverse events, but the difference was not significant.

Deaths, Serious Adverse Events and Withdrawn:

There were no deaths reported during the study. Seven patients were prematurely withdrawn from the study due to adverse events and none of them were attributed to the study medication by investigator. Three patients were from the Venofer group and 4 (one was withdrawn before start of study medication) from the Ferrlecit group. The following table summarizes the patients who were prematurely withdrawn from the study due to adverse events:

Patients withdrawn from the study due to adverse events

Treatment group	Patient number	Adverse event	Reason for withdrawal in final CRF
Venofer [®]	26	Gangrene, peripheral gangrene	Clinical event
	30	Angina pectoris	Clinical event
	56	Surgery	Clinical event
Ferrlecit [®]	11	Application site reaction	No reason available
	13	Fever (2x), Hypochromic anaemia#, Leukocytosis (2x)	No reason available
	25	Pneumonia*	Protocol violator
	55	Surgery	No reason available

* Reported before start of study medication.

Hypochromic anaemia (Costart term) [or drop in haemoglobin (Investigator's term)]

Sponsor's table in NDA Vol. 1.31, pp. 251

Three patients (3 mentions) in the Venofer group and 4 patients (6 mentions) in the Ferrlecit group had serious adverse events. The serious adverse events reported were as follows:

Serious adverse events

Treatment group	Patient number	Adverse event
Venofer [®]	26	Peripheral gangrene
	30	Angina pectoris
	56	Surgery
Ferrlecit [®]	11	Application site reaction
	13	Fever, Hypochromic anaemia, Leukocytosis
	25	Pneumonia*
	55	Surgery

* Reported before start of study medication.

Hypochromic anaemia (Costart term) [or drop in haemoglobin (Investigator's term)]

Sponsor's table in NDA Vol. 1.31, pp. 251

Clinical Laboratory Evaluation:

The following table summarizes the descriptive statistics for laboratory data:

Descriptive statistics for laboratory data

Variable [Unit]	Treatment group					
	Venofer [®]			Ferrelecit [®]		
	Base-line*	End-point	Change**	Base-line*	End-point	Change**
RBC count (Erythrocytes) [T/L]	3.6	3.5	-0.1	3.6	3.6	-0.0
Haematocrit [%]	35.6	35.1	-0.7	36.2	35.8	-0.2
MCH [PG]	31.6	32.4	0.8	31.6	31.8	0.3
MCHC [g/dL]	31.9	32.6	0.7	31.3	31.9	0.6
MCV [fL]	99.2	99.8	0.4	99.6	99.7	0.3
Hypochromic red blood cells	6.3	4.6	-2.0	10.8	5.2	-5.6
Reticulocytes [%]	21.8	19.9	-2.6	19.6	18.2	-1.1
Platelets [G/L]	223.8	250.5	28.5	227.6	230.3	-0.1
WBC count (Leukocytes) [G/L]	7.3	7.7	0.5	7.3	7.2	-0.1
Neutrophils [%]	66.8	66.4	1.0	62.6	64.6	1.9
Lymphocytes [%]	21.2	20.6	-1.6	22.2	21.2	-0.4
Monocytes [%]	5.7	6.7	0.4	6.5	7.6	1.1
Eosinophils [%]	4.7	3.8	-0.8	4.4	4.5	-0.4
Basophils [%]	0.6	0.5	-0.1	0.7	0.5	-0.2
Serum Iron (Total) [mcg/dL]	56.2	82.4	25.7	59.8	76.1	19.5
Serum transferrin [mcg/dL]	185.8	177.1	-7.7	168.6	162.4	-6.0
% transferrin saturation	21.9	33.3	10.9	25.7	34.4	9.5
SGOT/AST [U/L]	7.8	8.3	0.5	6.4	6.6	0.3
SGPT/ALT [U/L]	10.1	10.9	0.8	7.5	7.9	0.3
C-Reactive protein [mg/dL]	0.9	1.0	0.3	0.9	1.5	0.7

- * Mean value at Week 0
- * Mean value at endpoint (obtained by means of last observation carried forward)
- ** Endpoint - baseline

Sponsor's table in NDA Vol. 1.31, pp. 252

The following table summarizes the incidence rates (with incidences of more than 10%) of high abnormalities (i.e. values which were normal (within normal limits) or low (below normal limits) at baseline and changed to high (above normal limits) in any time during the study in the two treatment groups.

Incidence of high abnormalities

Variable	Treatment group	
	Venofer [®]	Ferrelecit [®]
MCV	4/ 8 (50%)	1/ 7 (14%)
MCH	6/ 18 (33%)	11/ 23 (48%)
WBC count (Leukocytes)	0/ 22 (0%)	6/ 26 (23%)
Neutrophils (total)	7/ 17 (41%)	8/ 23 (35%)
Monocytes	17/ 19 (89%)	12/ 12 (100%)
Eosinophils	6/ 14 (43%)	6/ 14 (43%)
Basophils	5/ 23 (22%)	5/ 25 (20%)
Reticulocyte Count	3/ 4 (75%)	9/ 9 (100%)
Hypochromic	1/ 9 (11%)	2/ 8 (25%)
C-Reactive Protein	9/ 11 (82%)	9/ 10 (90%)
SGPT/ALT	3/ 24 (13%)	0/ 23 (0%)
% transferrin saturation	9/ 23 (39%)	10/ 23 (43%)

Sponsor's table in NDA Vol. 1.31, pp. 253

The incidence rates of high laboratory abnormalities for leukocytes was 6/26 (23%) in the Ferrlecit group in comparison to 0/22 (0%) in the Venofer group.

The following table summarizes the incidence rates (with an incidence of more than 10%) of "low" abnormalities (i.e. values which were normal (within normal limits) or high (above normal limits) at baseline and changed to low (below normal limits) in any time during the study in the two groups.

Incidence of low abnormalities

Variable	Treatment group	
	Venofer [®]	Ferriect [®]
Haematocrit	7/ 9 (78%)	6/ 9 (67%)
Erythrocytes	5/ 5 (100%)	4/ 6 (67%)
MCHC	6/ 9 (67%)	6/ 7 (86%)
WBC count (Leukocytes)	4/ 23 (17%)	5/ 27 (19%)
Neutrophils (total)	3/ 21 (14%)	8/ 23 (35%)
Lymphocytes	2/ 5 (40%)	6/ 10 (60%)
Eosinophils	7/ 24 (29%)	8/ 25 (32%)
Basophils	10/ 14 (71%)	13/ 19 (68%)
Platelets	5/ 26 (19%)	5/ 26 (19%)
Serum Transferrin	5/ 8 (63%)	3/ 4 (75%)
Iron (Total Serum Iron)	1/ 23 (4%)	4/ 24 (17%)
% transferrin saturation	2/ 12 (17%)	9/ 18 (50%)

Sponsor's table in NDA Vol. 1.31, pp. 254

Vital Signs:

The following table summarizes the mean blood pressure (BP) and heart rate at baseline and endpoint:

Blood pressure (BP) and heart rate at baseline and endpoint

Variable	Treatment group					
	Venofer [®]			Ferriect [®]		
	Base-line ^a	End-point ^b	Change ^{cc}	Base-line ^a	End-point ^b	Change ^{cc}
Systolic BP (mmHg)	134.4	135.8	-1.1	144.7	143.8	-1.7
Diastolic BP (mmHg)	72.1	73.3	0.5	73.3	78.1	4.9
Pulse rate (beats/min)	74.0	76.8	3.4	74.0	70.9	-2.6

^a Mean value at Week 0

^b Mean value at endpoint (obtained by means of last observation carried forward)

^{cc} Endpoint - baseline

Sponsor's table in NDA Vol. 1.31, pp. 254

No significant changes from baseline to endpoint were observed. There were no differences between the two treatment groups.

7.2.4.3 Reviewer's Comments

Study Schaefer showed an unchanged mean hemoglobin level from baseline in both Venofer and Ferriect treatment groups. Also, there was no difference in hemoglobin level at end of treatment between the two treatment groups. This was a single center, open-label, nonrandomized trial. There were 22 (37.2%) patients who violated study inclusion/exclusion criteria at enrollment and additional 9 (15.2%) patients had protocol deviations during the study. The study results did not support the efficacy of Venofer use in hemodialysis patients. For safety results, the most frequent adverse events for Venofer in this study were infection, skin ulcer, pneumonia, and sinusitis. No patient died during the study. Three patients reported serious adverse events and discontinued treatment. These serious adverse events included gangrene, angina and surgery.

8. Clinical Studies in Other Populations

8.1 Trial 1: Study 50 (Vol. 1.37)

8.1.1 Study Protocol (Translation)

Title of the Study: Clinical Pilot Study of the Treatment of Anemia in Crohn's Disease with Intravenous Iron and Erythropoietin.

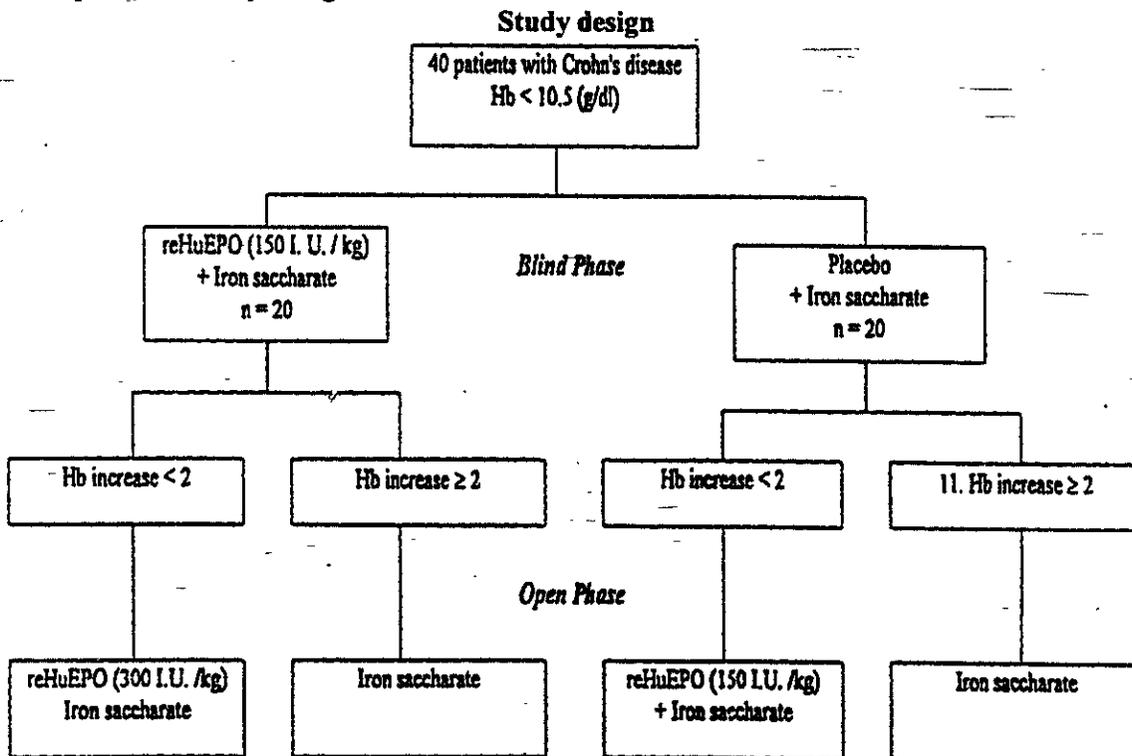
Study Investigators: Christoph Gasche, MD, Vienna University Hospital, Vienna, Austria

Study Period: 1993 - 1995

Study Objective: To compare the efficacy of intravenous iron hydroxysaccharate alone and that of combination of intravenous iron hydroxysaccharate and subcutaneous EPO in treatment of Crohn's disease associated anemia.

Study Design: This was a two-center, double-blind, randomized, parallel group controlled pilot study for EPO treatment. For intravenous iron hydroxysaccharate, the study design was a baseline-controlled study.

The sponsor's study design chart is shown below:



Sponsor's chart in ND/. Vol. 1.37, pp. 75

The study consisted of two study phases: blind phase for first 8 weeks followed by open phase for another 8 weeks. Patients were randomized to receive either intravenous iron hydroxysaccharate and rHuEPO or intravenous iron hydroxysaccharate and placebo for first 8 weeks in blind phase. The study then was unblinded at the end of 8 weeks and response to treatment was assessed. For patients who had responded to treatment (defined as hemoglobin increase ≥ 2 g/dl), rHuEPO (or placebo) was stopped. For patients who did not respond, the dose of rHuEPO was increased to 300 U/kg 3 times/week in rHuEPO group and rHuEPO was started at 150 U/kg 3 times per week in placebo group for additional 8 weeks.

Study Population: Inclusion criteria were patients with Crohn's disease according to the criteria of Maichow et al., hemoglobin ≤ 10.5 g/dl on 2 occasions within 4 weeks, age over 18 years and signed informed consent. Exclusion criteria were treatment with substances which influence blood formation, such as azathioprine or other immunosuppressives, severe course of Crohn's disease with the likely risk of complications such as stenosis, perforation, ileus, or abscess, inadequate patient compliance, a history of hypersensitivity to one of the preparations used, hemochromatosis or hemosiderosis, anamnestic proneness to thromboembolism, severe hypertension, or cardiovascular disease, existing vitamin B₁₂ or folic acid deficiency or other hematological disease, a serious concomitant disease which considerably impairs the prognosis and quality of life of the patient (e.g. tumor or serious organ lesions), or creatinine > 2 mg/dl.

Study Drug: Iron hydroxysaccharate (Veno-Ferrum-Hausmann®, Hausmann, St. Gallen, Switzerland) 200 mg was administered intravenously as infusion (2 ampoules of 100 mg in 250 ml NaCl over 60 minutes) twice weekly for the first two weeks then once weekly thereafter to all patients for a total of 16 weeks. IV iron infusion was withheld if transferrin saturation $> 50\%$ and restarted when transferrin saturation $< 30\%$.

Recombinant human erythropoietin (rHuEPO, Erypo®, Cilag AG, Vienna) 150 I.U./kg was administered subcutaneously 3 times/week to patients in rHuEPO group in the first 8 weeks in blind phase. For patients who had hemoglobin increase < 2 g/dl in the end of blind phase, rHuEPO dose was doubled in rHuEPO group and started at dose of 150 I.U./kg 3 times/week in placebo group for additional 8 weeks. For patients who had hemoglobin increase ≥ 2 g/dl in the end of blind phase, rHuEPO was stopped.

If a hemoglobin > 14 g/dl was achieved during the study, both therapies were stopped and the patient was evaluated as "responder".

Study Plan: The sponsor's study flow chart is shown below:

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Study flow chart

	Week of treatment																	
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Hb concentration, reticulocyte count	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ferritin level, transferrin level, transferrin saturation	X		X		X		X		X		X		X		X		X	
Vit. B ₁₂ , folic acid	X																	
Coombs-tests direct, indirect	X																	
C-reactive protein level	X		X		X		X		X		X		X		X		X	
Serum freezing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CDAI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of life	X								X									X
Safety (AE)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Sponsor's chart in NDA Vol. 1.37, pp. 64

Eligible consenting patients were enrolled in the study and were randomized into EPO treatment or placebo groups. All patients received iron hydroxysaccharate therapy. After 8 weeks of treatment, the first evaluation was carried out and the randomization code opened. The EPO dose was adjusted for all patients based on hemoglobin responses. The second evaluation was scheduled at the end of 16 weeks of treatment.

Data collected in the study included: hematology (complete blood count, reticulocyte count), iron studies (transferrin saturation, serum iron, ferritin), C-reactive protein (CRP), liver function, creatinine, vitamin B₁₂, folic acid, indirect Coombs test, Crohn's disease activity index (CDAI, a composite of 8 items: number of liquid or very soft stools, abdominal pain, general well-being, extraintestinal manifestation, use of opiates, abdominal mass, hematocrit and body weight), and quality of life scale (a composite of 9 items: feeling of well-being, mood, level of activity, pain, nausea, appetite, physical activity, social activities, and anxiety). The schedule for each assessment is shown in above chart.

Efficacy Parameters: Proportion of patients with increase of hemoglobin ≥ 2 g/dl and improvement of quality of life scale.

Safety Assessment: Adverse events were to be recorded at each check-up. In addition to the CDAI, the subjective well-being of the patients, particularly with regard to anemia symptoms, were to be recorded.

Statistical Methods: It was planned to enroll approximately 40 patients (20 in each group) in the study. The statistical method for efficacy analysis was not provided.

8.1.2 Study Results

Disposition of Patients:

Of the 40 enrolled patients, 20 patients in the placebo group and 19 patients in the rHuEPO group completed the first phase of the study (8 weeks of treatment). One patient in the rHuEPO group was withdrawn prematurely in the first phase due to noncompliance.

Demographic Data and Baseline Characteristics:

The demographic data and baseline characteristics of study patients are shown below:

Table 1 Baseline characteristics (mean±SD)

	Venofer [®] + Placebo	Venofer [®] + rHuEPO
Hemoglobin (g/dL)	8.7 ± 1.4	8.5 ± 1.5
Number of men	3	10*
CDAI	225 ± 88	220 ± 57
Quality of life score	22 ± 5	20 ± 4
Age (years)	31 ± 9	32 ± 15
Number of RBC-units received within the last 12 months	1.1 ± 2.0	0.5 ± 1.3
Prednisolone dose (mg/day)	13 ± 20	8 ± 13
Reticulocytes (% of RBC)	20 ± 11	20 ± 17
C-reactive protein (mg/dL)	2.7 ± 2.7	2.7 ± 3.2
Transferrin (mg/dL)	292 ± 70	332 ± 89
Transferrin saturation (%)	4.4 ± 3.5	4.1 ± 6.2
Ferritin (µg/L)	32 ± 50	15 ± 23
Serum EPO (U/l)	82 ± 88	129 ± 171

* p<0.05

Sponsor's table in NDA Vol. 1.37, pp. 56

The two treatment groups were comparable with regard to demographic data except for sex. Three male patients (15%) were included in the erythropoietin group compared with ten male patients (50%) in the placebo group (p<0.05). The ages of the patients ranged from 18 to 68 years. The type of Crohn's disease in patients were isolated small bowel disease (4 patients), colonic disease (4 patients), ileocolonic disease (27 patients), and ileocolonic disease with additional stomach or esophageal involvement (5 patients).

Efficacy Results:

At the end of 8 weeks of treatment, 15/20 patients in the placebo group (75%, 95% CI: 51% to 91%) and 18/19 patients in the rHuEPO group (95%, 95% CI: 74% to 100%) had hemoglobin level increase ≥2 g/dl (p = 0.20). The cumulative response (hemoglobin level increase ≥2 g/dl) rate was higher in the rHuEPO group (p = 0.036).

The followings are the sponsor's table and figure:

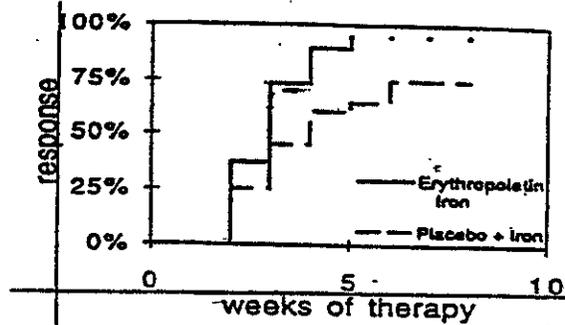
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Kaplan-Meier estimation of the cumulative response-rate in % to rHuEPO and iron therapy or to placebo and iron therapy

Table 2

Week of treatment	rHuEPO + Iron	Placebo + Iron
0	0	0
1	0	0
2	37	25
3	74	45
4	89	60
5	95	65
6	95	75
7	95	75
8	95	75

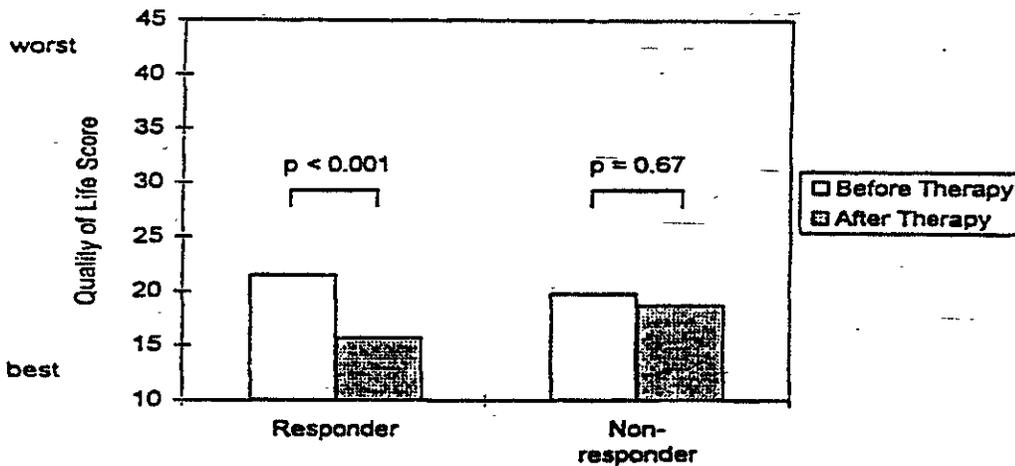
Figure 1



Sponsor's table and figure in NDA Vol. 1.37, pp. 57

At the end of first 8 weeks, the mean increase in hemoglobin from baseline was statistically significantly higher in the rHuEPO group (4.9 g/dl) compared to the placebo group (3.3 g/dL) ($p = 0.004$).

The sponsor indicated that increase of hemoglobin level was positively correlated with improvement of the quality-of-life-score and Crohn's disease activity index. The change of quality of life score is shown in the figure below:



Sponsor's figure in NDA Vol. 1.37, pp. 79

No detailed statistical analysis was provided for Crohn's disease activity index. C-reactive protein levels did not change significantly from baseline.

The increases in mean serum ferritin levels and mean transferrin saturation from baseline were statistically significantly lower ($p < 0.001$ for serum ferritin and $p = 0.032$ for transferrin saturation) in the rHuEPO group (mean serum ferritin increased 116 $\mu\text{g/L}$ and mean transferrin saturation increased 5%) compared to the placebo group (mean serum ferritin increased 282 $\mu\text{g/L}$ and transferrin saturation increased 10%). The patients who did not respond to the treatment (1 in the rHuEPO group and 5 in the placebo group) had

normal ferritin levels (mean of 298 µg/L) and low transferrin saturation (mean of 9%) at the end of this 8 week treatment period.

A total of 33 responders (15 placebo group and 18 rHuEPO group) after the first 8 week were treated with I.V. iron alone during the second 8 weeks (open phase). At the end of 16 weeks, 27 of the 33 responders (14 in rHuEPO group and 13 in placebo group) had changes in hemoglobin concentration of less than 2 g/dL, 3 (1 in rHuEPO group and 2 in placebo group) had a further increase (mean of 2.4 g/dL) and 3 (all in rHuEPO group) had a decrease in hemoglobin concentration (mean of - 2.5 g/dL).

All previous nonresponders showed an increase in hemoglobin between week 8 and week 16 (increase of 3.6 g/dL in 1 patient in rHuEPO group, 3.6 g/dL with 95%CI of 2.5 to 4.6 g/dL in 5 patients in placebo group).

Safety Assessment

A total of 14 patients (7 in the rHuEPO group and 7 in the placebo group) reported one or more adverse events. Six different types of adverse events were noted. One of these six AEs was related to the erythropoietin injection as local burning at the site of injection. The other five AEs were related to the iron(III)-hydroxide sucrose complex infusion: burning at the site of venipuncture (3), bitter taste (2), body temperature $\geq 38^{\circ}\text{C}$ (3), transient hypotension (2), and transferrin saturation increase $>50\%$ (2). No serious AE were reported. Other unrelated adverse events considered by the investigator were not recorded in the sponsor's data.

8.1.3 Reviewer's Comments

Study 50 (Gasche) was a pilot study and the objective of study was to compare the efficacy of intravenous iron hydroxysaccharate alone and that of combination of intravenous iron hydroxysaccharate and subcutaneous EPO in treatment of Crohn's disease associated anemia. All patients received the intravenous iron hydroxysaccharate therapy. Compared to baseline, hemoglobin increased ≥ 2 g/dl at the end of 8 weeks of treatment in 75% patients in iron hydroxysaccharate therapy alone and 95% patients in combination therapy of iron hydroxysaccharate and EPO. The mean increase in hemoglobin from baseline in patients who received only Venofer treatment (200 mg 18 doses) was 3.3 g/dl. However, this study did not provide evidence of stable baseline hemoglobin and stable Crohn's disease condition to support baseline and end-of-treatment comparison. In addition, the sponsor did not provide detailed data on other treatments used in study patients for improvement of Crohn's disease condition during the study. The major deficiencies of the study included:

- 1) The study objective was to evaluate the efficacy of EPO treatment in combination with iron hydroxysaccharate therapy in patients with Crohn's disease associated anemia and not to evaluate the efficacy of the iron hydroxysaccharate therapy.
- 2) The sponsor did not provide evidence of stable baseline hemoglobin level to support baseline and end of treatment comparison.
- 3) The sponsor did not provide evidence of stable Crohn's disease condition at baseline to support baseline and end of treatment comparison.

- 4) Collection of safety data was incomplete. The sponsor did not record all adverse events including unrelated adverse events considered by the investigator.

8.2 Trial 2: Study 52 (Vol. 1.38)

Study Protocol

The study protocol is not available.

8.2.1 Study Report

Title of the Study: Intravenous iron gluconate or iron saccharate for patients with malabsorption or oral iron intolerance.

Study Investigators: S. Bulvik, MD and I. Zeitlin, MD, Laniado Hospital, Netanya, Israel

Study Period: 1993-1998

Study Objectives: To evaluate the efficacy and safety of iron(III)-hydroxide sucrose complex (Venofer) and iron gluconate (Ferlecit®) in the treatment of iron deficiency anemia in patients with malabsorption or intolerance to oral iron.

Study Design: This was a single center, open-label, nonrandomized, concurrent treatment controlled study. Patients were serially selected to receive iron gluconate (Ferlecit) (group A) or iron (III)-hydroxide sucrose complex (Venofer) (group B). Total treatment was 10 infusions for each iron preparation. The responses of hematology and iron indices were evaluated at the end of treatment.

Study Population: A total of 121 patients participated in the study (50 in group A and 71 in group B). Inclusion criteria were patients with iron deficiency anemia due to malabsorption or intolerance to oral iron, age between 18 and 70 years, ferritin <50 ng/ml, hemoglobin <10 g/dl, and informed consent. Exclusion criteria were breastfeeding, drug or alcohol abuse, lack of cooperation, or participation in another clinical trial within 3 months before or during this study.

Study Drug:

Group A: Patients were given iron gluconate (Ferlecit, _____) 125 mg diluted in 500 ml of 0.9% sodium chloride administered over 3 hours. A total of 10 infusions were given at intervals of 1 to 7 days.

Group B: Patients were given iron(III)-hydroxide sucrose complex (VENOFER®, Vifor (International) Inc) 100 mg diluted in 500 ml 0.9% sodium chloride over 3 hours. A total of 10 infusions were given at intervals of 1 to 7 days.

Study Plan:

The study consisted of screening, enrollment, following-up in 4 weeks and final visit in 8 weeks. Baseline information collected at screening visit included informed consent, medical history, physical examination, and clinical laboratory tests: hematology (hemoglobin, hematocrit, erythrocytes, hypochromic erythrocytes, mean cell volume, mean cell Hb content, mean cell Hb concentration, leukocytes, platelets), iron studies (serum ferritin, iron, TIBC), liver enzymes (GOT, GPT, GGT), and creatinine.

Eligible patients were serially selected to receive Venofer or Ferrlecit treatment. A follow-up visit and final visit included repeated clinical laboratory tests and assessment of adverse events.

Efficacy Parameters:

Hemoglobin, hematocrit, erythrocytes count, serum ferritin, iron, and TIBC.

Safety Assessment:

All adverse events (AEs) were to be documented at each visit, along with the description of the event, time and duration, severity, and outcome. Vital signs were also to be recorded at each scheduled visit.

Statistical Methods:

Mann-Whitney test was used to compare efficacy parameters between groups. Wilcoxon test was used to compare efficacy parameters between different visits in the same group.

8.2.2 Study Results:

Disposition of Patients:

Of the 121 enrolled patients, 44 patients did not complete the treatment. The following table summarizes the patient disposition in the study:

Patient disposition

	Group A (Ferrlecit)	Group B (Venofer)
Patients enrolled	50	71
Patients completed	33	44
Patients withdrawn	17	27
Reasons for withdrawn		
Adverse events	10	17
Patients refusal	7	6
Others	0	3
Iron stores replenished	0	1

Reviewer's table based on the sponsor's data in NDA Vol. 1.38, pp. 119-121

Seven patients in Ferrlecit group and 6 patients in Venofer group refused to receive further treatment during the study and the reasons for refusal were not provided in the study report and data.

Demographic and baseline characteristics:

The demographic and baseline characteristics in the two treatment groups are shown below:

Table 1: Demographic data (mean ± SD)

	Group A iron gluconate 50 patients	Group B iron(III)-hydroxide sucrose complex 71 patients
Age (years)	37.7±13.4	38.3±12.1
Sex. (M/F)	3/46 1 unknown	5/62 4 unknown
Body Mass Index (kg/m ²)	24.7±2.8	25.0±3.3
Systolic Blood Pressure (mmHg)	104.9±13.0	109.2±13.8
Diastolic Blood Pressure (mmHg)	65.1±8.6	67.6±9.1
Anaemic for (days)	478.6±623	702.0±762.8
Hospitalised at screening (yes/no)	4/43 3 unknown	5/62 4 unknown

Sponsor's table in NDA Vol. 1.38, pp. 120

There were 25 patients who had malabsorption of oral iron and 106 patients who had intolerance to oral iron. The underlying diseases of the iron deficiency is shown in the following table:

Table 2: Iron deficiency anaemia history (incl. multiple responses)

	Group A iron gluconate 50 patients	Group B iron(III)-hydroxide sucrose complex 71 patients
Anaemia due to malabsorption of oral iron	9	16
Inflammatory bowel disease	3	7
Celiac disease	1	1
Gastric surgery	3	3
Others	2	4
Anaemia due to intolerance of oral iron	46	60
Pregnancy	23	26
Upper gastrointestinal tract bleeding	15	31
Gastritis	8	11
Lower gastrointestinal tract bleeding	5	3

Sponsor's table in NDA Vol. 1.38, pp. 120

At baseline, the patients in group A (Ferri-lecit) had statistically significantly lower hemoglobin (8.2±1.3 vs. 8.7±1.1, p<0.01) and hematocrit (26.1±3.5 vs. 27.4±3.1, p=0.045) than patients in group B (Venofer). The study results may be biased by these differences at baseline in favor of Venofer treatment.

Efficacy Results:

The mean of hemoglobin, hematocrit, erythrocytes, serum ferritin and iron values was statistically significantly higher at the final visit than that at baseline in both groups. Comparison between groups did not show any statistically significant difference at final visit for these parameters.

The results are shown below:

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Table 3: Comparison of haematological parameters (mean ± SD)

	Group A iron gluconate		Group B iron(III)-hydroxide sucrose complex	
	Baseline	Final visit	Baseline	Final visit
Haemoglobin (g/dL)	8.16±1.34	11.33±1.48 ***	8.74±1.09	11.75±1.42 ***
Haematocrit (%)	26.07±3.48	34.64±4.10 ***	27.40±3.06	35.63±3.8 ***
Erythrocytes (10 ⁶ /mm ³)	3.68±0.60	4.29±0.55 ***	3.85±0.48	4.41±0.51 ***
Serum Ferritin (µg/mL)	6.71±4.79	109.3±79.4 ***	6.53±5.23	84.0±64.5 ***
Iron (mmol/l)	33.7±18.9	95.0±43.0 *	27.0±13.6	62.0±28.8 **
TIBC (µg/dL)	475.5±95.5	447.7±125.0	438.1±97.7	391.7±69.0
MCV (fl)	72.6±8.4	80.8±7.0 ***	72.4±8.3	80.1±11.3 ***
MCH (pg)	22.6±3.4	26.3±2.8 ***	22.6±3.4	27.4±7.3 ***
MCHC (g/l)	31.0±2.2	32.4±1.4 **	31.3±1.5	32.8±1.3 ***

* p<0.05 baseline vs. final visit

** p<0.01 baseline vs. final visit

*** p<0.001 baseline vs. final visit

No significant difference was found between treatment groups at the final visit.

Sponsor's table in NDA Vol. 1.38, pp. 121

For above hemoglobin comparison, 121 patients were included at baseline and 102 patients (43 in Ferrlecit group and 59 in Venofer group) were included at final visit (based on data in NDA Vol. 1.38, pp. 165, 217). It was noted that there were 104 patients with hemoglobin value available at final visit based the sponsor's data listing (NDA Vol. 1.38, pp. 307-308). Two patients with hemoglobin available at final visit were not included in the efficacy analysis and no reasons were provided in the study report.

There was no difference in MCV, MCH and MCHC values between groups at baseline or the final visit, whereas statistically significant increases in all three parameters were observed between baseline and final visit in both groups.

Safety Assessment:

In total 15 patients in Group A (Ferrlecit) and 25 patients in Group B (Venofer) reported one or more adverse events.

The following table summarizes the adverse events in the two treatment groups:

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Table 4: Adverse events

Organ system / Symptom	Group A iron gluconate (n=50)		Group B iron(III) sucrose (n=71)	
	No. of Patients	No. of AE	No. of Patients	No. of AE
Body as a Whole - General Disorders				
Anaphylaxis	1	1		
Chills	1	1		
Feeling Cold			1	2
Flank Pain (rt.)	1	1		
Flush			1	1
Obesity	1	1	2	2
Weakness	3	5		
Skin and Appendages Disorders				
Cellulitis			1	1
Pruritus	1	2	1	3
Rash Skin	2	3	1	1
Urticaria	1	1		
Musculo-skeletal System Disorders				
Back Pain	2	3		
Muscle Pain			1	2
Central & Periph. Nervous System				
Bad Dreams			1	1
Dizziness	3	7	9	20
Headache			2	6
Loss of Concentration			1	2
Gastrointestinal System Disorders				
Abdominal Discomfort	1	1		
Abdominal Pain	3	5	7	17
Diarrhoea	1	2	3	5
Heartburn			1	3
Nausea			1	1
Vomiting			2	2
Cardiovascular Disorders. General				
Oedema (leg)	1	1		
Heart Rate & Rhythm Disorders				
Palpitation	1	1		
Vascular (Extracardiac) Disorders				
Phlebitis			2	3
Respiratory System Disorders				
Dyspnoea			1	1
Total	15	35	25	73

Sponsor's table in NDA Vol. 138, pp. 122

In group A, 27 AEs (77%) were considered as possibly or probably related to the treatment with iron gluconate (e.g. abdominal pain, diarrhea, weakness, pruritus & rash) by investigators; six (17%) AEs were rated as "certain" (anaphylaxis, back pain, dizziness, and abdominal discomfort); and 2 (6%) AEs were as "unlikely" (flank pain & weakness). In group B (iron sucrose), 48 (66%) AEs were considered by the investigators as possibly or probably related to the treatment (dizziness, headache, abdominal pain, diarrhea, heartburn); 24 (33%) AEs were considered as certainly related (feeling cold, pruritus, muscle pain, dizziness, headache, loss of concentration, abdominal pain, diarrhea, phlebitis, dyspnea); and 1 (1%) AE (nausea) was as unlikely related to the treatment. The sponsor indicated that the report was based on data which was collected/analyzed retrospectively and causality assessment was done retrospectively by the investigators.

Two patients in group A and 5 patients in group B discontinued treatment after the first iron infusion due to adverse events while 8 in group A and 12 in group B withdrew later during the study due to adverse events. The following table listed the patients who discontinued treatment due to adverse events:

Table 5: Adverse events that led to premature discontinuation, including multiple responses

	Group A (iron gluconate)	Group B (iron(III)-hydroxide sucrose complex)
Withdrawal after first infusion	back pain (pat.no. 37)	vomiting (pat.no. 60, 126)
	anaphylaxis (pat.no. 137)	diarrhoea (pat.no. 60)
		bad dreams (pat.no. 63)
		cellulitis (pat.no. 85)
		dizziness (pat.no. 126, 140)
		abdominal pain (1 pat.no. 40)
Withdrawal during study	skin rash (pat.no. 6)	abdominal pain (pat.no. 75, 99, 131, 134, 135, 59)
	dizziness (pat.no. 107, 16)	dizziness (pat.no. 80, 71, 116, 118, 135)
	weakness (pat.no. 16, 41, 56)	head ache (pat.no. 83, 131)
	diarrhoea (pat.no. 21)	diarrhoea (pat.no. 99)
	abdominal pain (pat.no. 21)	flush (pat.no. 59)
	leg oedema (pat.no. 41)	obesity (pat.no. 67)
		loss of concentration (pat.no. 116)
		jaundice (pat.no. 118)

Sponsor's table in NDA Vol. 1.38, pp. 122

8.2.3 Reviewer's Comments

Study 52 (Bulvik) was a single center, nonrandomized, open-label, parallel controlled study in 123 patients with iron deficiency anemia who had malabsorption and intolerance to oral iron. No study protocol was available. Study 52 did not demonstrate superiority of Venofer over Ferrlecit in treatment of iron deficiency anemia ($p > 0.05$) and was not specifically designed as an equivalence or non-inferiority trial. Venofer group had significantly higher hemoglobin and hematocrit than Ferrlecit group at baseline that may bias the result in favor of Venofer. The study showed a significant increase in mean hemoglobin from baseline in Venofer group ($p < 0.001$). However, the study did not provide stable baseline hemoglobin to support baseline and end of treatment comparison. The major deficiencies of the study included:

- 1) The study did not demonstrate superiority of Venofer over Ferrlecit with regard to efficacy. The study was not specifically designed as an equivalence or non-inferiority trial.
- 2) The sponsor did not provide evidence of stable baseline hemoglobin to support baseline and end of treatment comparison.
- 3) The study protocol is not available.
- 4) This was a nonrandomized study.
- 5) The mean baseline hemoglobin levels were not comparable between groups. Patients in Ferrlecit group had statistically significantly lower hemoglobin (8.2 ± 1.3 vs. 8.7 ± 1.1 , $p < 0.01$) and hematocrit (26.1 ± 3.5 vs. 27.4 ± 3.1 , $p = 0.045$) than patients in Venofer group. (bias in favor of Venofer)

6) Many patients (44 patients, 36.3%) did not complete the study.

9. Integrated Review of Safety

The sponsor provided 74 reports/publications (34 end stage renal disease [ESRD], 40 other causes of anemia) and included 4099 patients who received at least 1 dose of iron sucrose. Only 13 ESRD reports/publications (1111 patients) and 18 reports/publications of anemia of other causes (1151 patients) reported at least one adverse event in the study reports. Forty-three studies either had no safety reported (5 ESRD, 5 other causes of anemia), all adverse events not specified or quantified (4 ESRD, 9 other causes of anemia), or no adverse event (12 ESRD, 8 other causes of anemia). The following table summarizes the overall studies [LU98001 study (77 patients) is not included in the table]:

Table 99 Breakdown of the Presence of Adverse Events in Studies

Adverse Event Reporting	Reference Number	Total Patients	Patients on Iron Sucrose
Studies Without Quantified Adverse Events			
No reference to safety	ESRD: 11, 13, 29, 30, 33	198	162
	Other: 57, 59, 68, 73, 76	287	68
		Subtotal: 485	Subtotal: 230
Exact number of adverse events not specified or only select adverse events reported	ESRD: 9, 19, 27, 28	858*	801*
	Other: 43, 44, 45, 46, 48, 51, 63, 64, 66	410	341
		Subtotal: 1268	Subtotal: 1142
Studies With Quantified Adverse Events			
Studies with 0 adverse events reported for iron sucrose	ESRD: 3, 4, 5, 7, 10, 12, 17, 21, 22, 25, 31, 32	495	342
	Other: 37, 53, 56, 58, 62, 67, 74, 75	159	123
		Subtotal: 654	Subtotal: 468
Studies with at least 1 adverse event reported	ESRD: 1, 2, 6, 8, 14, 15/16, 18, 20, 23, 24, 26, 69	1062	1034
	Other: 36, 38, 39, 40, 41, 42, 47, 49, 50, 51, 52, 54, 55, 60, 65, 70, 71, 72	1409	1151
		Subtotal: 2471	Subtotal: 2185
Total Number of Patients without Safety Data			
ESRD		1056	963
Other		802	409
All Studies		1858	1372
Total Number of Patients with Safety Data			
ESRD		1557	1376
Other		1568	1274
All Studies		3125	2650
Total Number of Patients			
ESRD		2613	2339
Other		2376	1683
All Studies		4983	4022
Ongoing Studies	ESRD: 34, 35	341	341

a: Actual total number of unique patients is unclear in Ref. [27]. 704 patients over 4 years were analyzed, but some patients may have been included in more than 1 year.
ESRD: End stage renal disease.

Sponsor's table in NDA Vol. 1.40, pp. 295

9.1 Extent of Exposure

Extent of exposure to iron sucrose in patients with end stage renal disease is summarized in the following table. The total cumulative iron dose data were available in 21 studies and 1150 patients.

Table 100 Summary of Extent of Exposure to Iron Sucrose in ESRD

Reported Iron Doses	No. Patients (%) Dosed	
	Number of Patients Dosed ^a	% Patients by Dose
Dose Administered (mg Iron)^b		
20 mg	33	2%
50-200	144	10%
100 mg	393	29%
200 mg	429	31%
250 mg	27	2%
300 mg	218	16%
400	35	3%
500 mg	80	6%
300-800	17	1%
Total No. Patients Treated	1376	
Maximum Total Cumulative Dose (mg Iron)^c		
200	109	11%
300	189	19%
400	35	4%
500	22	2%
800	7	<1%
900	29	3%
1000	67	7%
>1000-1200	217	22%
>1200-2000	241	24%
>2000	83	8%
Total No. Patients Reported	999	

a: Number of patients is maximized for each dose or range; actual number of patients receiving total dose or maximum of range was not necessarily reported.
b: Extracted from references: 20 mg [18]; 50-200 mg [15/16, 20]; 100 mg [1, 2, 3, 4, 5, 8, 10, 21, 26, 32]; 200 mg [7, 12, 14, 22, 23, 24, 31, 69]; 250 mg [6,]; 300 mg [25, 69]; 400 mg [69]; 500 mg [8, 69]; 300-800 mg [17].
c: Extracted from references: 200 mg [12, 69]; 300 mg [69]; 400 mg [69]; 500 mg [69]; 800 mg [22]; 900 mg [25]; 1000 mg [2, 14, 26]; >1000 - 1200 [3, 4, 20, 23, 31, 32]; >1200-2000 [1, 6, 7, 18, 22, 24]; >2000 [12, 21.]

Note: LU98001 study (77 patients) is not included in the table
Sponsor's table in NDA Vol. 1.40, pp. 296

Extent of exposure in other studies is summarized in the following table:

Table 101 Extent of Exposure for Other Studies

Reported Iron Doses	No. Patients (%) Dosed	
	Number of Patients Dosed ^a	% Patients by Dose
Dose Administered (mg Iron): Adult Patients^b		
30-200	24	2%
50 mg	11	<1%
50-200	17	1%
100 mg	632	42%
100-200	120	8%
200 mg	436	29%
400	47	3%
500-525 mg	164	11%
700-800	67	4%
Total No. Patients Treated	1518	
Total Cumulative Dose (mg Iron): Adult Patients^c		
100	99	9%
>100 - <1000	307	29%
1000	148	14%
>1000-1500	198	19%
>1500-2000	205	19%
>2000	96	9%
Total No. Patients Reported	1053	
Dose Administered (mg Iron): Pediatric Patients^d		
1.5 mg/kg/day	8	18%
3 mg/kg/day	16	36%
6 mg/kg/week	21	47%
Total No. Patients Treated	45	
Total Dose Administered (mg Iron): Healthy Subjects^e		
50	11	24%
100	19	42%
400	15	33%
Total No. Patients	45	

a: Number of patients is maximized for each dose or range; actual number of patients receiving total dose or maximum of range was not necessarily reported.
b: Extracted from references: 30-200 [60]; 50 mg [59]; 30-200 mg [67]; 100 mg [38, 41, 43, 44, 46, 52, 57, 58, 61, 62, 63, 64, 65, 67, 70, 71, 75]; 100-200 mg [37]; 200 [36, 39, 42, 45, 47, 48, 49, 50, 51, 70,]; 400 [70]; 500-525 [70, 72]; 700-800 [70, 72]
c: 100 mg [70, 75,]; <1000 mg [39, 44, 46, 48, 70]; 1000 mg [42, 52, 64, 66, 78]; <1000-1500 [37, 38, 47, 57, 59, 67]; >1500-2000 [37, 45, 60, 63, 70]; >2000 [48, 50, 51, 65, 68].
d: 1.5 mg/kg/day [56]; 3mg/kg/day [53]; 6mg/kg/week [54].
e: 50 mg [73]; 100 mg [74, 76]; 400 mg [70].

Sponsor's table in NDA Vol. 1.40, pp. 297

9.2 Demographics of Patients Who Exposed to Iron Sucrose

Demographics for patients with end stage renal disease are summarized in the following table:

Table 102 Summary of Demographics for ESRD Patients Treated with Iron Sucrose

	Number of Patients (n=2339)	Percent Distribution for Reported Data
Range of Mean Ages by Decades Reported^a:		
34	109	22.4%
42-44	180	37.3%
53-59	174	36.0%
60	20	4.1%
Total Reported	483	
Range of Ages:		
16-92	1405	
Range Maximum ≤65 years	144	10.2%
Range Maximum >65 years	1261	89.8%
Sex^b:		
Males	964	53.5%
Females	837	46.5%
Total Reported	1801	
Race^c:		
White	66	36.3%
Black	39	21.4%
Asian	7	3.8%
Other	70	38.5%
Total Reported	182	

a: References for mean ages reported: 34 years [8]; 42-44 [1, 4, 17, 32]; 53-59 [2, 3, 5, 6, 13, 18, 31]; 60 [12]; ranges: ≤65 years [8, 69]; >65 years [1, 2, 4, 6, 14, 17, 27, 31, 69]

b Sex reported in references [1, 2, 3, 4, 5, 6, 8, 12, 13, 14, 15/16, 17, 18, 20, 21, 22, 27, 31, 32].

c: Race reported only in references [1], [2], and [6].

ESRD: End stage renal disease.

Note: LU98001 study (77 patients) is not included in the table;

^c for race was mistyped as ^a;

Other race represented coloured in South Africa or Hispanic.

Sponsor's table in NDA Vol. 1.40, pp. 298

Demographics for patients in other studies are summarized in table below:

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Table 103 Summary of Demographics for Other* Patients Treated with Iron Sucrose

	Number (%) of Patients by Study Type with Reported Data							Total
	Pregnancy/ Postpartum ^b	Autologous Blood Donation ^c	Gastro- intestinal Disorders ^d	Rheumatic Diseases ^e	Pediatrics ^f	Early Studies ^g	Healthy Subjects ^h	
	N (%)	N (%)	N (%)	N (%)				
Range of Mean Ages (Years):								
<1					73 (82%)			73 (11%)
1-18					16 (18%)			16 (2%)
20-29	302 (100%)					8 (19%)		310 (48%)
30-39			131 (100%)			15 (36%)		146 (22%)
40-49		22 (32%)		6 (33%)		19 (45%)		47 (7%)
50-59				12 (67%)				12 (2%)
60-69		46 (68%)						46 (7%)
Total Reported	302	68	131	18	89	42	0	650
Reported Age Range:								
Newborn -17					111			111 (20%)
18-43	113							113 (21%)
13-90		129	60	29		85	19	322 (59%)
Range Maximum ≤65	302	0	20	6	111	51	19	509
Range Maximum >65	0	129	40	23	0	34	0	226
Sex:								
Males	0	75 (39%)	31 (24%)	4 (8%)	34 (47%)	24 (22%)	3 (25%)	171 (13%)
Females	717 (100%)	117 (61%)	96 (76%)	45 (92%)	39 (53%)	86 (78%)	9 (75%)	1109 (87%)
Total Reported	717	192	127	49	73	110	12	1280
<p>a: Includes all patients/subjects treated with iron sucrose included in studies of anemia of other causes (ie, excluding ESRD study patients). b: References for ages reported: [36, 70,]; references for sex: [36, 37, 38, 39, 40, 41, 70, 71]. c: References for ages reported: [42, 43, 44, 46, 48, 49]; references for sex [42, 43, 44, 45, 46, 48, 49]. d: References for ages reported: [37, 53, 54]; references for sex [37, 53, 54]. e: References for ages reported: [57, 59, 75]; references for sex [37, 57, 59, 75]. f: References for ages reported: [41, 53, 54, 55, 56] references sex: [41, 54]. g: References for ages reported: references for sex [60, 62, 63, 64, 65, 67, 68, 72]; race reported only in reference [67], 15 white patients. h: No mean ages reported; references for sex [70, 74, 76]. ESRD: End stage renal disease.</p>								

Sponsor's table in NDA Vol. 1.40, pp. 299

9.3 Safety in Patients with End Stage Renal Disease

Integrated safety results from the three pivotal clinical studies

Extent of exposure:

The three pivotal trials included 231 patients who received at least one dose of Venofer treatment. Among those, 70 (91%) patients in LU98001 and 20 (87%) patients in LU98002 received Venofer 100 mg 10 doses, and 111 (85%) patients in VIFOR/001 received total treatment dose as scheduled according to baseline hemoglobin and weight. The following table summarizes the mean dialysis sessions and mean total Venofer doses received in the three trials.

Extent of Exposure in Pivotal Trials

Studies	Venofer doses	Mean dialysis sessions	Mean total doses received
LU98001	100 mg	9.8±1.1	983.1±105.6 mg
LU98002	100 mg	9.7±1.1	969.6±106.3 mg
VIFOR/001	100 mg	14.8±4.6	1480 mg

Reviewer's table

Seventy-two (94%) patients in LU98001 and 19 (83%) patients in LU98002 received all Venofer doses as undiluted injection over 5 minutes. The remaining 9 patients in the two trials and all 131 patients in VIFOR/001 received Venofer doses diluted in 100 ml 0.9 sodium chloride infused over approximately 30 minutes. In VIFOR/001 trial, a test dose (50mg in 2.5 ml diluted in 50 ml 0.9 sodium chloride infused over 5-15 minutes) was required for all patients within 2 weeks before the study enrollment.

Common adverse events:

A total of 185 (80%) patients reported at least one adverse event in 231 patients in three pivotal studies (LU98001, LU98002 and VIFOR/001). The most common adverse events of Venofer treatment were hypotension (39%), Cramps (27%), nausea (17%), headache (12%), vomiting (9%), chest pain (7%), dizziness (7%), diarrhea (6%), abdominal pain (5%), and hypertension (5%). The following table summarizes the adverse events reported in three pivotal studies:

Summary of adverse events reported in three pivotal studies

Organ system and event	LU98001	LU98002	VIFOR/001	Total
Number of patients	77	23	131	231
Total number of Patients with at least one adverse event during and following the treatment period	50 (65%)	18 (78%)	117 (89%)	185 (80%)
Body as a whole				
Headache	3 (4%)	4 (17%)	21 (16%)	28 (12%)
Unwell			6 (5%)	6 (3%)
Fever/pyrexia	1 (1%)		7 (5%)	8 (4%)
Malaise	1 (1%)		4 (3%)	5 (2%)
Flu symptoms			3 (2%)	3 (1%)
Asthenia	2 (3%)	4 (17%)		6 (3%)
Gangrene		1 (4%)		1 (0.4%)
Infection	1 (1%)	2 (9%)		3 (1%)
Pain	8 (10%)	2 (9%)		10 (4%)
Injection site hemorrhage	1 (1%)	1 (4%)		2 (1%)
Sepsis	1 (1%)	1 (4%)		2 (1%)
Face edema	1 (1%)	1 (4%)		2 (1%)
Chills	1 (1%)			1 (0.4%)
Accidental injury	5 (6%)			5 (2%)
Sleepiness			1 (1%)	1 (0.4%)
Cardiovascular system				
Hypotension	12 (16%)	8 (35%)	70 (53%)	90 (39%)
Chest pain	2 (3%)		13 (10%)	15 (7%)
Hypertension	4 (5%)		7 (5%)	11 (5%)
Vascular access problem			3 (2%)	3 (1%)
Angina pectoris	1 (1%)	1 (4%)	1 (1%)	3 (1%)
Myocardial infarction	1 (1%)			1 (0.4%)
Arrhythmia	1 (1%)			1 (0.4%)
Congestive heart failure	1 (1%)			1 (0.4%)
Palpitation			2 (2%)	2 (1%)
Tachycardia			2 (2%)	2 (1%)
AV fistula clot/clotting			2 (2%)	2 (1%)
Peripheral vascular disorder	1 (1%)			1 (0.4%)
Postural hypotension	1 (1%)			1 (0.4%)

Digestive system				
Nausea	3 (4%)		35 (27%)	38 (17%)
Vomiting		2 (9%)	18 (14%)	20 (9%)
Nausea and vomiting		1 (4%)		1 (0.4%)
Raised liver enzymes			8 (6%)	8 (4%)
Abdominal pain	6 (8%)		6 (5%)	12 (5%)
Diarrhea	7 (9%)	1 (4%)	5 (4%)	13 (6%)
Raised GGT			4 (3%)	4 (2%)
Hepatic congestion			3 (2%)	3 (1%)
Constipation	2 (3%)			2 (1%)
Hemorrhagic colitis	1 (1%)			1 (0.4%)
Gastroenteritis	1 (1%)			1 (0.4%)
GI bleeding	1 (1%)		2 (2%)	3 (1%)
Endocrine system				
Hypocalcemia	1 (1%)			1 (0.4%)
Hypoglycemia	1 (1%)			1 (0.4%)
Parathyroid disorder	1 (1%)			1 (0.4%)
Hemic and lymphatic system				
Ecchymosis	1 (1%)			1 (0.4%)
Thrombocytopenia	1 (1%)			1 (0.4%)
Drop in hemoglobin			6 (5%)	6 (3%)
Blood loss on dialysis			2 (2%)	2 (1%)
Epistaxis			2 (2%)	2 (1%)
Leukopenia			2 (2%)	2 (1%)
Neutropenia			2 (2%)	2 (1%)
Metabolic and nutritional system				
Peripheral edema	2 (3%)			2 (1%)
Edema	1 (1%)			1 (0.4%)
Hypervolemia		1 (4%)	5 (4%)	6 (3%)
Hypovolemia	1 (1%)			1 (0.4%)
Musculoskeletal system				
Cramps/leg cramps	3 (4%)	1 (4%)	58 (44%)	62 (27%)
Musculoskeletal pain			8 (6%)	8 (4%)
Neck pain	1 (1%)			1 (0.4%)
Neck rigidity	1 (1%)			1 (0.4%)
Back pain	1 (1%)		2 (2%)	3 (1%)
Gout			2 (2%)	2 (1%)
Joint pain			2 (2%)	2 (1%)
Arthritis			1 (1%)	1 (0.4%)
Myasthenia		1 (4%)		1 (0.4%)
Tendosynovitis			1 (1%)	1 (0.4%)
Nervous system				
Dizziness	2 (3%)	4 (17%)	9 (7%)	15 (7%)
Anxious	1 (1%)	1 (4%)		2 (1%)
Subdural hematoma	1 (1%)			1 (0.4%)
Hypertonia	2 (3%)	1 (4%)		3 (1%)
Respiratory system				
Cough			5 (4%)	5 (2%)
Asthma	1 (1%)			1 (0.4%)
Hemoptysis	1 (1%)			1 (0.4%)
Pneumonia	1 (1%)		5 (4%)	6 (3%)
Dyspnea	2 (3%)	2 (9%)	3 (2%)	7 (3%)
Upper respiratory infection			3 (2%)	3 (1%)
Pleural effusion	1 (1%)		1 (1%)	2 (1%)
Pharyngitis/sore throat		1 (4%)	2 (2%)	3 (1%)
Chest infection			2 (2%)	2 (1%)
Rhinitis		1 (4%)		1 (0.4%)
Respiratory disorder	2 (3%)			2 (1%)
Tuberculosis			1 (1%)	1 (0.4%)
Sensory disorder				
Abscess ear/Purulent discharge ear			2 (2%)	2 (1%)
Amblyopia	1 (1%)			1 (0.4%)
Taste perversion	1 (1%)	1 (4%)		2 (1%)
Skin and appendages				
Pruritus	2 (3%)	1 (4%)	6 (5%)	9 (4%)
Rash		1 (4%)	2 (2%)	3 (1%)

Application site reaction	8 (10%)	1 (4%)		9 (4%)
Skin ulcer	1 (1%)			1 (0.4%)
Cellulitis	1 (1%)			1 (0.4%)
Necrosis	1 (1%)			1 (0.4%)
Sweating		1 (4%)		1 (0.4%)
Urogenital system				
Dysuria	1 (1%)		2 (2%)	3 (1%)
Graft rejection			2 (2%)	2 (1%)
Urinary tract infection			2 (2%)	2 (1%)
Vaginitis	1 (1%)			1 (0.4%)
Nephrectomy site problems			2 (2%)	2 (1%)

Reviewer's table

Serious adverse events:

Overall, 3 patients died in three pivotal trials. The cause of death in one patient was considered due to hypoglycemia reaction or myocardial infarction, one due to coumadin necrosis, and one due to rejection of renal transplant. All deaths were not considered related to study drug by investigator. A total of 42 patients (18%) experienced serious adverse events during the study in three pivotal trials. The most common serious adverse events were pneumonia (3%), vascular access problem (2%), GI bleeding (1%), cellulitis (1%), pleural effusion (1%), hypoglycemia (1%), chest pain (1%), angina pectoris (1%), sepsis (1%), graft rejection (1%), and accidental injury (1%). The following table summarizes the serious adverse events in three pivotal studies:

Summary of serious adverse events reported in three pivotal studies

Organ system and event	LU98001	LU98002	VIFOR/001	Total
Number of patients	77	23	131	231
Total Number of Patients experienced serious adverse event	19 (25%)	3 (13%)	20 (15%)	42 (18%)
Death	2		1	3 (1%)
Vascular access problem	3		1	4 (2%)
Cellulitis	1		1	2 (1%)
Severe pleural effusion	1		1	2 (1%)
Tuberculosis			1	1 (0.4%)
Pneumonia	1		5	6 (3%)
Hypoglycemia	1		1	2 (1%)
Salpingo-oophoritis			1	1 (0.4%)
Chest pain			2	2 (1%)
Uveitis			1	1 (0.4%)
GI bleeding	1		2	3 (1%)
Hypotension			1	1 (0.4%)
Graft rejection			2	2 (1%)
Hernia repair			1	1 (0.4%)
Hemiparesis			1	1 (0.4%)
Renal transplant			1	1 (0.4%)
Nephrectomy site problem			1	1 (0.4%)
Endophthalmitis			1	1 (0.4%)
Myocardial infarction	1			1 (0.4%)
Sepsis	1	1		2 (1%)
Parathyroid disorder	1			1 (0.4%)
Necrosis/Coumadin necrosis	1			1 (0.4%)
Gastroenteritis	1			1 (0.4%)
Angina pectoris	1	1		2 (1%)
Hemorrhagic colitis	1			1 (0.4%)
Accidental injury	2			2 (1%)
Congestive heart failure	1			1 (0.4%)
Infected pilonidal cyst	1			1 (0.4%)
Gangrene		1		1 (0.4%)

Reviewer's table

Discontinuations due to adverse events:

A total of 9 patients discontinued Venofer treatment permanently due to adverse events in three pivotal trials (1 in LU98001 and 8 in VIFOR/001). These adverse events were severe diarrhea, graft rejection (2 patients), GI bleeding, neutropenia, tiredness, renal transplant, drop hemoglobin, and nephrectomy site problem. The treatment was discontinued temporarily in 5 patients in LU98001 due to adverse events including severe diarrhea (2 patients), application site reaction, malaise, and fistula repair.

Anaphylactoid reaction:

No life-threatening or serious anaphylactic/anaphylactoid reaction was reported in three pivotal trials. Five patients (2.2%) developed pruritus, urticaria, or rashes after Venofer treatment and were considered as anaphylactoid reactions (1 in LU98001, 2 in LU98002 and 2 in VIFOR/001). There were six patients with dyspnea without other clinical information in three trials; it was not possible to determine if those were due to anaphylactoid reactions. Hypotension was not defined in three trials and it was not clear that hypotension was caused by dialysis or anaphylactoid reaction in these studies. Overall, no patient discontinued treatment due to above reactions. It should be noted that all 131 patients in VIFOR/001 required a negative test dose before enrollment, which could underestimate the incidence of anaphylactoid reaction in this study (1.5%). Based on LU98001 and LU 98002, the incidence of anaphylactoid reaction was 3%.

Safety information from published studies

The sponsor provided 3 other study reports without data listing and 24 publications (including abstracts).

Macdougall IC, Chandler G, Armstrong A, Breen C, Harchowal J, Cavill I. Characterisation of iron availability from three different IV iron preparations in dialysis patients. Final report. 5.3.1999.

In this study report, 20 patients were given a single dose of 200 mg iron sucrose. Iron sucrose was compared to iron dextrin (20 patients) and iron dextran (20 patients) in this study. No adverse events were observed in patients who received the single injection of iron sucrose; however, 3 patients had anaphylactic reactions to iron dextran in this study.

Danielson BG. Supplementation with IV iron sucrose complex in patients with renal anemia. Internal report. 10 December 1993a, b

The author conducted 2 studies in anemic dialysis patients. The first study was a pilot study and the same patients were subsequently enrolled in the larger study. One hundred ten patients received an initial 50 mg dose of iron as iron sucrose followed by 100 mg of iron 1-3 times weekly. In the pilot study of 20 patients who received iron sucrose, no adverse events occurred. The larger study was conducted over a 7-year period. Of the 110 patients who received iron sucrose for an average of 12 months (range 2-48 months), only 4 patients reported adverse events (1 metallic taste; 1 nausea and vomiting; 1 fever; and 1 exanthema on arms, legs and trunk).

Chandler G, Harchowal J, Macdougall I. Intravenous iron(III)-hydroxide sucrose complex: establishing the optimum dose given as an infusion over two hours. Internal Report. 6.1.1998

In the dose tolerability study by Chandler, anemic ESRD (including predialysis, on hemodialysis, chronic ambulatory peritoneal dialysis or transplant patients) patients 22-82 years of age were administered single doses of 200, 300, 400, or 500 mg iron as iron sucrose intravenously over 2 hours. A total of 335 patients were enrolled in this study. Good tolerance was observed in the 89 patients who received the 200 mg iron dose and in the 189 patients who received the 300 mg dose. No adverse events were reported for these patients. Among the 35 patients who received the 400 mg iron dose, two (6%) patients reported a total of 7 adverse events: one patient reported hypotension, abdominal and lower back pain, nausea and vomiting and one patient reported nausea and vomiting. Among the 22 patients who received 500 mg iron as iron sucrose, 8 (36%) patients reported adverse events: hypotension reported in 8 patients was accompanied by nausea (3 patients), lower back pain (1 patient), back pain (1 patient), and bilateral edema of hands and feet (1 patient). Two patients who received 500 mg iron and one patient who received 400 mg iron were hospitalized for 24 hours for their hypotension. Two patients in the 500 mg group had their infusions of iron sucrose discontinued due to adverse events (hypotension, nausea and vomiting; hypotension, bilateral edema). The adverse events observed in the 400 and 500 mg dose groups may related to transient iron overload indicated by the sponsor.

Among the 24 publications, only 8 studies with at least one adverse event reported. The following table summarizes the adverse events from those 8 studies:

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Table 109 Summary of all Safety Reported for ESRD Patients Treated with Iron Sucrose in 24 Published Studies

Study Author [Ref.]	Number of Patients Treated with IV Iron Sucrose	Dose of Iron (mg)	Adverse Events (AEs) Adverse Drug Reactions (ADRs)
Studies with AEs Reported: 8 Studies (N=455)			
Al-Momen et al. [8]	58	500 mg/week (1-2 doses)	5 patients: 2 fever, headache, nausea, hypotension, and urticaria after treatment 3 headache, nausea, and skin discomfort during infusion
Silverberg et al. [14]	51	3 x 100 mg/week (5-10 doses)	no AEs observed
	34	200 mg/month	1 patient: sweating and nausea during infusion of test dose
Silva et al. [18]	33	3 x 20 mg/week	4 patients: metallic taste
Nyvad et al. [20]	34	Cumulative dose of 1150 in doses of 50-200 mg	1 patient: swelling of tongue and lips, pruritus, & an urticarial exanthema 2 days after first dose; iron-sucrose was withdrawn
Erten et al. [9]	26	100 mg post dialysis/dialysis session (x 10) then	no AE observed
	21	100 mg/week for 6 months 10 x 100 mg post dialysis (x 10 dialysis)	1 patient: discontinued due to abdominal pain and hypotension after infusion ^a
Jones et al [24]	98	100 mg test dose then 200 mg/week	2 patients: wheezing following 100 mg test dose (withdrawn due to this AE.) ^a ; hypotension following 200 mg dose
D'Souza et al. [23]	90	200 mg/week for 6 weeks	2 patients: erythematous rash ^a
Mestrez et al. [26]	10	100 mg/dialysis (x 10 dialysis sessions)	1 patient: nausea, vomiting & hypotension during infusion of the first dose

^a Personal communication to Vifor (International), Inc

Sponsor's table in NDA Vol. 1.40, pp. 312

Thirteen (2.9%) patients reported anaphylactoid reactions during and after the infusion of study drug in 455 hemodialysis patients in the 8 published studies and these reactions included urticaria/skin discomfort (8), wheezing (2), hypotension (3).

9.4 Safety in Other Populations

The sponsor provided 40 publications including abstracts in other studies. A total of 19 studies with at least one adverse event were included.

The following table summarizes the adverse events in those 19 studies:

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Adverse events reported from 19 publications in other studies

Study Author (Reference #)	Study Patients	Iron Sucrose Received	Adverse Events Reported
Al-Momen (36)	52 pregnant women	200mg (unknown dose)	fever(1), injection site reaction (1)
Chamate (37)	120 women with iron deficiency anemia (pregnant, puerperium, miscarriage and other reasons)	100mg (1 dose) and 200mg (5 doses)	headache (3), tachycardia (3), paresthesia (1), abdominal pain (1)
Polatti (38)	30 pregnant women	100mg (14 doses)	phlebitis (3), headache (1), tachycardia (1)
Breymann (39)	11 pregnant women	200mg (4 doses)	metallic taste (4), facial flush (1)
Lebrecht (40)	36 pregnant women	400mg (1 dose)	paresthesia in legs (1)
Zimmerman (41)	90 postpartum women	100mg (1 dose)	metallic taste (27), warm sensation (2)
Beris (42)	45 nonanemic patients who need autologous blood donation for anticipated elective surgery	200mg (5 doses)	weakness (8), dizziness (5), headache (1), nausea (1), hypotension (1), palpitation (1), angina (2), dyspnea (1)
Tryba (47)	100 anemic patients anticipated orthopedic surgery	300mg (3 doses)	phlebitis (7)
Weisbach (49)	30 nonanemic patients who need autologous blood donation for anticipated elective surgery	200mg (1-4 doses)	injection site reaction (1), muscular pain (2), pain in jaw (1), dizziness (1), headache (1), abdominal pain (3), nausea (4), diarrhea (4), angina (1), dyspnea (1)
Gasche (51)	20 ulcerative colitis	200mg (18 doses)	injection site reaction (4), diarrhea (2)
Meyer (54)	21 premature infants	6mg/kg (4 doses)	necrotizing enterolitis (1), infection (1), bronchopulmonary dysplasia (1) vomiting and abdominal distention (1)
Michaud (55)	14 anemic children (11 months-17 years)	unknown	allergic reaction (1)
Paschen (60)	4 iron deficiency anemia	200mg	injection site reaction (2)
Pasquel (65)	8 iron deficiency anemia	100mg (3-43 doses)	vomiting (1), anebiasis of liver (1)
Huch (70)	15 healthy volunteers 393 pregnant or postpartum women	2000mg (2 doses) 100mg-2000mg (1 dose)	flush (2), injection site reaction (1); nausea (2), vertigo (1), limb pain (1); metallic taste (17), flush (14), injection site reaction (6), nausea (6), itching exanthema (3), sweating (2), tachycardia (1), vertigo (1), hypotension (1), abdominal pain (1), calf cramps (1), hypotension and collapse (1).
Fassa (71)	5 pregnant women	unknown	vertigo (1)
Auakov (72)	5 anemic patients 21 anemic patients	700-800mg 500mg	headache, vomiting, nausea and transient collapse (3) headache and nausea (2)

Reviewer's table based on the sponsor's data in NDA Vol. 1.40, pp. 314-326; Vol. 1.36-1.39, 1.41

9.5 Post-Marketing Safety

Report on the Use of Iron Sucrose under Compassionate Use Sales in South Africa:
Between 11/18/1993 and 1/14/1997, 414 patients with iron deficiency anemia received a total of — ampules of 100 mg iron as iron sucrose on a "compassionate use" basis. Of the 414 patients, safety data was documented for 160 patients. Three patients (1.9% of the documented cases, 0.72% of all cases) developed anaphylactoid reactions believed by the manufacturer to be due to a dosage exceeding the recommended maximum dose (7

mg/kg body weight or 500 mg iron); these were treated with corticosteroids and/or antihistamines. All three patients made a full recovery. A fourth patient receiving an infusion of 500 mg of iron in form of iron sucrose developed severe bronchospasm and urticaria that required corticosteroids. In summary, a total of 20 patients (12.5% of the documented cases; 4.8% of all cases) reported 38 adverse events. The incidence and severity of adverse reactions were believed to be dose-related. The other 34 reactions were of moderate or mild severity and consisted of: pruritus, rash, urticaria, swelling or edema of the hands and feet, nausea, diarrhea, stomach cramps, breath shortness associated with joint stiffness, tiredness and pain or irritation at the infusion site.

Post-Marketing Safety Surveillance:

A summary of safety reports on iron sucrose for 1992 through 1997 (Report No. PVZ-8000-E03; 1998) was provided by Vifor (International) Inc. The following table lists the adverse events reported in Switzerland, where iron sucrose is registered, and in various European countries and South Africa, where the product is available on a "named patient" basis with a more strict and established legal requirement to report adverse events. Special attention was given to anaphylactoid reactions.

The reported adverse events consisted of adverse events previously reported with iron sucrose. Taking into account all prescriptions of iron sucrose within this time frame of 5 years, more than _____ ampules corresponding to more than 51,000 patients treated, the observed adverse events were reported at a frequency of 0.07%. Among the 53 reports, 9 anaphylactoid reactions in 9 patients were attributed primarily to either too rapid administration or overdose of iron sucrose (0.017%) by Vifor.

The summary of adverse reactions in the following table from the pharmacovigilance report includes the six cases reported in Switzerland to the Swiss Center of Pharmacovigilance (5 cases) and Vifor (International) Inc. (1 case) during the period of 1992-1996.

Additionally, a review of the Swiss Center of Pharmacovigilance cases (_____ 1997) identified two further cases reported outside of this period. One case presented an anaphylactic reaction in 1988 and the other case showed paresthesia and swelling of the hands in 1997. All patients recovered without sequelae.

Outside of the report period 1992-1997, in 1974, a pregnant woman died of an embolus following the injection of an outdated (11 years of age) ampoule of iron sucrose. This event was believed by Vifor most probably caused by the presence of sediment in the preparation which had long expired. Another fatal reaction was reported in 1976 after administration of a second 100 mg dose of iron sucrose to a 78-year-old woman suffering from emphysema. No additional information on the age of the ampoule or on the patient's pathology is known indicated by Vifor.

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Table 118 Pharmacovigilance Data of Iron Sucrose Reported Between 1992-1997 From Countries With a Strict Pharmacovigilance System

Country	Time frame	Iron sucrose® 5 ml ampules	Estimated number of patients	Adverse events (AEs) No. of AEs/No. of patients with AEs	Number of anaphylactoid reactions
Belgium	1995 - 1996	————	6,713	none	0
Denmark	1993 - 1996	————	933	2 AEs / 2 patients: non-serious anaphylactoid reactions	2
Finland	1995 - 1997	————	946	2 AEs / 2 patients: anaphylactoid reactions	2
France	1995 - 1997	————	324	3 AEs / 3 patients: 1 urticaria, 2 paravenous injections	0
Netherlands	1996	————	795	none	0
Norway	1994 - 1996	————	1,100	none	0
South Africa	1993 - 1997	————	414	38 AEs / 20 patients: muscle pain, vomiting, abdominal pain, diarrhea, headaches, arthralgia, pruritus, rash, urticaria, swelling or edema of hands or feet, nausea, joint stiffness, tiredness, pain at infusion site, localized irritated veins, bronchospasm, breathless, palpitation, tachycardia, thorax pain, and hypertension	3 ¹
Sweden	1992 - 1996	————	11,373	2 AEs / 2 patients: sensory disturbance in arm following 5th injection (extravasation), nausea and vomiting	0
Switzerland	1992 - 1996	————	23,314	6 AEs / 6 patients: flush, urticaria, myalgia, collapse, anaphylactoid reactions (2), joint pains and headache, nausea, heart rate elevation, cramps, and syncope	2 ²
Turkey	1995 - 1996	————	4,767	none	0
UK and Ireland	1995 - 1996	————	1,137	none	0
Total	1992 - 1997	————	51,816	53 AEs / 35 patients	9

¹Due to a too fast infusion/injection which resulted in a short term overload of the patients' iron transport system.

²Due to massive overdose.

Sponsor's table in NDA Vol. 1.40, pp. 357

Periodic Safety Update Report (PSUR) by Manufacturer Vifor (International) Inc.
For period of 10/31/1997 to 4/30/1998 (Report No. PVZ-8001-E01:1998):

A total of 91,775 patients received iron sucrose in clinical trials and commercially worldwide within this report period. During this period, 21 patients (0.02%) reported 33 adverse events post-marketing and 22 patients reported 46 adverse events in clinical trials and publications. Vifor indicated that there was no increased frequency of unlisted

reactions, no change in the characteristics of the listed reactions, no serious unlisted reactions, no overdoses (other than three cases of a slightly higher daily dose than recommended), no abuse, and no misuse. One anaphylactoid reaction (originally described as an anaphylactic reaction) and one allergic reaction were reported.

For a period of 2/28/1998 to 8/31/1998 (Report No. PVZ-8002-E01; 1998):

A total of 167,470 patients were exposed to iron sucrose within this report period. During this period, 31 patients (0.02%) reported 63 reactions postmarketing and 25 patients reported 35 adverse events in clinical trials and publications. One patient (Patient 1#03#01# 1999-4) was considered by the investigator to have had an overdose of iron sucrose (300 mg iron in 300 mL normal saline over 90 minutes). Approximately 24 hours after the infusion, the patient experienced stomach pains/cramps lasting 3 to 4 days. Although the most probable cause leading to the occurrence of these reactions was attributed to overdosage by the treating health professional (but not the sponsor), the patient did not really receive an overdose based on the patient's weight, 45 kg. This weight allowed the patient to receive a maximum single dose of 315 mg iron. Vifor indicated there was no increased frequency of unlisted reactions, no change in the characteristics of the listed reactions, no overdoses (other than 12 cases of higher daily dose than recommended), no abuse and no misuses, and one serious unlisted reaction (collapse, weakness and dizziness 1 #09# 1 # 1998-7) during the report period.

For a period of 9/1/1998 to 2/28/1999 (Report No. PVZ-8002-E02; 1999)

A total of 99,786 patients were estimated to have been exposed to iron sucrose in clinical trials and commercially within this period. During this time, 10 patients (0.01%) reported 35 adverse events that were at least possibly related to iron sucrose. There was no increased frequency of unlisted reactions, no change in the nature of the listed reactions, no significant overdoses (other than one case of higher daily dose than recommended and three cases of too rapid infusion of solution), no abuse and no misuses, and no serious unlisted reaction. Two anaphylactoid reactions were reported among the estimated 99,786 patients exposed to iron sucrose during this period.

Seven additional cases had been documented and reported to the manufacturer in 1996 and 1997 but had not been included in the previous safety updates for iron sucrose (Report Nos. PVZ-8000-E03, 1998 [79]; PVZ-8001 -E01, 1998 [81]; and PVZ-8002-E01, 1998 [82]). These seven cases were included in the most recent update (Report No. PVZ8002-E02; 1999 [83]) even though the events did not occur in the period covered by the report. Three of the seven cases (1#03#3#1996-08, 1#10#3#1996-10, and 1#05#3#19978) were anaphylactoid reactions.

Vifor indicated that a total of 17 anaphylactoid reactions have been reported out of 367,727 patients exposed to iron sucrose (relative incidence of 0.0046%) from their safety spontaneous reports.

Data by the WHO Collaborating Center for International Drug Monitoring:

A search was performed at the WHO Collaborating Center for International Drug Monitoring (Uppsala, Sweden) yielding all reactions reported under the key word

'Saccharated Iron Oxide', which includes iron sucrose. The sponsor indicated that the majority of the adverse events in the report were attributed to saccharated iron oxide preparations other than Venofer. The sponsor indicated that as of the date of the report (14 September 1995), Venofer® was neither registered nor sold on a compassionate use (named patient) basis in the countries listed in the report, except Switzerland.

According to the WHO search, a few cases of anaphylactic shock and anaphylactoid reactions, dyspnea, hypotension and circulatory failure have occurred. Adverse reactions at the site of injection were rarely observed. One case of syncope was reported from Switzerland, which is also mentioned in the Pharmacovigilance report from 1997 (PVZ8000-E03; 1998).

In the search, adverse reactions reported from Germany included: circulatory failure (13), anaphylactic shock (10), dyspnea (3), angioedema (3), vomiting (3), coma (2), apnea (2), abdominal pain (2), nausea (2), cardiac arrest (2), fecal incontinence (2), pallor (2), anxiety (1), sweating (1), hypotension (1), dystonia (1), vertigo (1), allergic reactions (1), agitation (1) and somnolence (1). The sponsor indicated that Venofer was not commercially available in Germany during this period, while several other preparations which utilized a similar or identical active component were available from 1968 onwards. The sponsor indicated that considerable differences might exist in product specification and characteristics (e.g., complex stability, molecular size etc.) for similar products.

Other Safety Data:

Previous reports from the 1950s in the UK mentioned severe reactions to iron sucrose (Ferrivenin, a formulation of an iron sucrose used in the UK which is not Venofer). Various initial doses from 25 mg up to 900 mg of Ferrivenin were used. Barfit and Swain (1953) reported a fatal case of a patient with iron deficiency anemia receiving Ferrivenin as a slow IV injection of 5 ml (100 mg iron) of iron sucrose.

9.6 Safety Update

The sponsor submitted the fourth periodic safety update report from Vifor (International) Inc. and one study publication.

Periodic safety update report (PSUR) for period of 3/1/1999 to 8/30/1999:

The report included safety result from clinical trials and market experience.

Patients in clinical trials

The number of patients exposed in clinical trials has been obtained from monitoring and status reports, final study reports and publications. A total of the 204 newly included patients from clinical trials or new publications within the period of this PSUR were considered for the patient exposure. Out of these newly included 204 patients, 122 were HD/CAPD patients (hemodialysis or continuous ambulatory peritoneal dialysis), 33 postpartum women, 30 rheumatoid arthritis patients, 10 premature infants, 6 children, and 3 inflammatory bowel disease patients.

Market Experience

The number of patients world-wide exposed to the product was calculated from the amount of ampoules sold assuming that one patient requires ampoules Venofer (containing 100mg iron each) per year. In the period between 1 March 1999 and 31 August 1999, ampoules (containing 100mg iron each) were sold by Vifor (International) Inc. This figure corresponds to 120,187 patient years and patients for the 6 month period (Table 3). Vifor indicated that some countries were not listed in Table 3 because the product was not distributed during the six-month report period or has been voluntarily withdrawn from the market by the authorization holder due to commercial considerations.

Of these ampoules sold, ampoules (corresponds to 14,880 patient years/patients) were used under a Named Patient Basis in 16 countries. In these countries the distributor has maintained close contact with the physicians prescribing Venofer. Therefore, there is accurate information on the number of units supplied and the occurrence of adverse events.

Table 3: World-wide patient exposure (patient years/patients for 6 months)

Country	Patient Years/ Patients	Country	Patient Years/ Patients	Country	Patient Years/ Patients
Egypt *	127	Finland *	386	Panama	745
Argentina	9412	France	443	Peru	1076
Austria *	997	Germany	648	Portugal	4486
Australia *	0	Greece *	4990	Romania	885
Belgium *	2759	Guatemala	1446	Saudi Arabia	2660
Bolivia	106	Haiti	191	Slovenia	867
Brazil	34517	Hungary *	225	Slovakia	411
Bulgaria	295	Iceland *	62	South Africa *	58
Canada *	1439	India	1528	Sri Lanka	50
Chile	633	Iran *	79	Sweden *	2013
China	247	Ireland *	209	Switzerland	3061
Cuba	13	Israel	1406	Taiwan	11455
Columbia	419	Lebanon	451	Thailand	165
Cyprus	57	Mexico	2015	Tunisia	18
Denmark *	758	Netherlands	1515	Turkey	10305
Domin. Republic	1481	Nicaragua	0	UK	6179
Ecuador	2015	Norway *	570	Uruguay	1225
El Salvador	310	Pakistan *	179	Venezuela	2600
				Patient years/ Patients for 6 months	120,187²

* countries in which patients are treated on a Named Patient Basis
² sum of all patient years/patients listed in table 3 = 120,190 (rounding error due to conversion from ampoules to estimated patient years/patients for each individual country)

Sponsor's table in NDA Vol. 14.1, pp. 13

Between 1 March 1999 and 31 August 1999 120,391 patients were exposed to Venofer in clinical trials and through the market.

Among the 120,187 patients (estimated on the basis of sold ampoules) who received Venofer between 1 March 1999 and 31 August 1999 through market exposure, 19 patients were reported to have experienced 87 adverse reactions at least "possibly-related" to Venofer. Vifor indicated that the majority of reactions were either adverse

reactions listed in the summary of product characteristics or isolated cases (8 of the 19 cases were serious ones).

Three patients out of the 204 patients exposed to Venofer in clinical trials (including reports from literature) were recorded to have experienced 4 adverse reactions in association with Venofer. None of these reactions were serious ones. Two of these 4 reactions were listed (2 x metallic taste in one patient) and 2 were unlisted (1 pruritus and 1 chills).

A review of the combined reports received from patient exposure, clinical trials and literature during this six-month report period indicates that the following 7 unlisted symptoms (all nonserious) have occurred: tiredness, chills, change of consciousness, diarrhea, arthralgia of knees, exanthema papulopustulosum corporis et faciei, and pruritus. All of the 7 non-serious unlisted symptoms occurred only once. These events have not been added to the summary of product characteristics. Vifor indicated that above events have been identified for continued observation in the future.

Concerning anaphylactoid reactions, out of 120,391 patients exposed to Venofer, one anaphylactic and 8 anaphylactoid reactions were reported within the six month-period. Vifor indicated that the anaphylactic reaction is actually an anaphylactoid reaction. Of the 9 anaphylactoid reactions, 6 were serious (anaphylactic shock, loss of consciousness, dilated pupil, hypotension, dyspnea or convulsion) and 3 were nonserious reactions. In all cases all symptoms rapidly resolved without sequel. The reaction was listed and a statement was included in the summary of product characteristics (October 1999) that facilities for cardiopulmonary resuscitation must be available when administering the product because allergic and anaphylactoid reactions and hypotensive episodes may occur. Vifor indicated that a test dose is currently required before administration of the first dose in a new patient for added security.

In summary, Vifor indicated that during the six-month period of this report there was no increased frequency of unlisted reactions, no change in the nature of the listed reactions, no serious unlisted reactions, 2 overdoses, no abuse and no misuse. In 3 cases there was too rapid an infusion time. Two cases of over-dilution were reported.

Vifor indicated that cumulatively, 27 anaphylactoid reactions have been reported out of 488,118 patients exposed to Venofer, a relative incidence of 0.0055% from spontaneous report.

Publication

The sponsor submitted one publication and others have been included in the safety update report.

Macdougall IC, Channderler G, Elston O and Harchowal J. Beneficial effects of adopting an aggressive intravenous iron policy in a hemodialysis unit.

In this study, 116 patients in hemodialysis unit received 100 mg iron sucrose as a bolus injection over 1-2 minutes at each dialysis session for 12 months. Adverse events reported in the article were only 2 cases of metallic taste in mouths. The author indicated

that incidence of infection and mortality rates in the study 12-month period were similar to previous year in the unit.

9.7 Safety Reports from IND Submissions

A total of 8 serious adverse events have been reported to FDA from IND (Venofer) submission between 9/1/1999 to 8/1/2000. These events include 4 deaths: two of them were due to cardiac arrest and other two were due to necrotizing enterocolitis in pre-term infants. The following table lists the available information. No additional information was provided for these cases at the time of review.

Safety reports from IND between 9/1/1999 to 8/1/2000

Patients	Adverse events	Underlying condition	Previous exposure	Treatment and reactions	Relationship to Venofer
45 M India	Death: Cardiac arrest 9/16/99	Chronic renal failure and anemia	Received 2 previous infusion without incident	One ampoule of Venofer (100mg) diluted in 250 ml normal saline was given over 1-2 hours. At some point after the infusion, 200 mg hydrocortisone was given to the patient by a nurse and then cardiopulmonary resuscitation without success. The latency between the event and the end of infusion is unknown	Not related. No autopsy was performed
middle age M India	Death: cardiac arrest 9/20/99	Pyrexia of unknown origin (controlled) and anemia (Hb:4g/dl)	No previous exposure	One ampoule of Venofer (100mg) diluted in 500 ml normal saline was administered. Five minutes after the beginning of the infusion, the patient became symptomatic and the infusion was stopped. The patient died 3-5 hours later of a sudden cardiac arrest.	Not related No autopsy was performed.
48 F UK	Hospitalization 8/25/1999	Renal failure and anemia	Previous infusion with adverse events (pain/stiffness in shoulders, hips, thighs, paraesthesia)	In 35 minutes of infusion (? end of), patient had abdominal pain, myalgia (thigh), nausea, erythema of face and neck, urticaria on limbs, hypertension for duration of 12 hours. Patient received hydrocortisone 100 mg iv and antihypertensive medication. Patient recovered without sequel. The drug was stopped.	Certainly related
≤80 days, unknown French	Death: necrotizing enterocolitis	Pre-term infant weighing ≤ 1.25 kg	No	In an investigator-driven study in French, patient was given venofer at 7 mg/kg /wk. No other information is available.	Not provided
≤80 days, unknown French	Death: necrotizing enterocolitis	Pre-term infant weighing ≤ 1.25 kg	No	In an investigator-driven study in French, patient was given venofer at 7 mg/kg /wk. No other information is available.	Not provided
≤80 days, unknown French	Necrotizing enterocolitis: Required intervention to prevent permanent impairment/damage.	Pre-term infant weighing ≤ 1.25 kg	No	In an investigator-driven study in French, patient was given venofer at 7 mg/kg /wk. No other information is available.	Not provided
≤80 days, unknown French	Necrotizing enterocolitis Required intervention to prevent permanent impairment/damage.	Pre-term infant weighing ≤ 1.25 kg	No	In an investigator-driven study in French, patient was given venofer at 7 mg/kg /wk. No other information is available.	Not provided
≤80 days, unknown French	Necrotizing enterocolitis Required intervention to prevent permanent impairment/damage.	Pre-term infant weighing ≤ 1.25 kg	No	In an investigator-driven study in French, patient was given venofer at 7 mg/kg /wk. No other information is available.	

Reviewer's table

10. Financial Disclosure

The sponsor has provided two certifications that no financial arrangements with an investigator, who conducted clinical study LU98001 or LU98002, have been made where outcome affects compensations (Form FDA 3454). For other studies, the sponsor did not provide certification.

11. Reviewer's Discussion

The sponsor has submitted NDA 31-135 to support Venofer use for the following 4 indications:

- 1) Dialysis associated iron deficiency anemia.

11.1 Overall Efficacy Assessment

For indication for treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy:

The sponsor submitted 3 pivotal studies (LU98001, LU98002 and VIFOR/001) and 4 supportive studies (Al-Momen, Yavuz, Hussain and Schaefer) in a total of 488 hemodialysis patients to support this indication. LU98001 was a multicenter, open-label, historically-controlled study and LU98002 and VIFOR-001 were multicenter, open-label, baseline-controlled studies. The mean hemoglobin level and change from baseline for the three pivotal studies are summarized in the following table:

Mean hemoglobin levels and changes from baseline for pivotal studies in ITT population

Pivotal Studies	Number of patients	Venofe dose (100 mg) received (mean±SEM)	Hemoglobin at Baseline (mean±SEM)	Hemoglobin at end of treatment (mean±SEM)	Hemoglobin Change (mean±SEM)
LU98001 Venofer	77	9.8±1.1	10.3± 0.12	11.3± 0.15	1.0± 0.12 (95% CI: 0.80-1.29)
Historical control	18	None	11.3± 0.16	11.3± 0.17	0.0± 0.21 p=0.0085
LU98002	23	9.7±1.1	10.38±0.19	11.52±0.27	1.14±0.20 (95% CI: 0.75-1.57) p=0.0003
VIFOR/001	130	14.7±4.8	7.2±1.6 (SD)	9.0±2.0 (SD)*	1.74±0.17 Mean ratio: 124% p<0.0001

*: post-study (1 month after completion of treatment)

SEM: standard error of mean; SD: standard deviation

Reviewer's table

The pivotal study LU98001 demonstrated a significant increase in hemoglobin level after Venofer treatment compared to patients with matched ferritin level at baseline in the historical control (p=0.0085). LU98002 and VIFOR/001 showed a significant increase in hemoglobin after Venofer treatment from baseline, which was consistent with the result in LU98001 study. The treatment effect of Venofer was about 1 g/dl increase in hemoglobin after 1 g iron given as Venofer injection in 10 dialysis sessions over 4 weeks,

which was observed in two pivotal studies conducted in the U.S. (LU98001 and LU98002).

The sponsor also submitted 4 supportive studies in hemodialysis patients. All 4 studies were single center, open label, nonrandomized, concurrent controlled study. The primary efficacy results for supportive studies are summarized in the following table:

Study design and efficacy results in supportive studies

Studies	Study design	# of patients	Venofer scheduled	Study result: Hemoglobin (g/dl)
Al-Momen	Group A: IV iron sucrose Group B: no iron	Group A: 53 Group B: 70	100mg 12 doses	Group A: 12.67±0.84 Group B: 11.98±0.56 p<0.001
Yavuz	Group I: IV iron sucrose Group II: no iron	Group I: 17 Group II: 13	100mg 3 times/wk x 4 wks then weekly or monthly per ferritin	Group I: 11.30±1.72 Group II: 9.18±2.16 p=0.017
Hussain	Group I: IV iron sucrose Group II: oral iron	Group I: 10 Group II: 10	100mg weekly 12 doses	Group I: 11.6±0.7 Group II: 10.6±1.2 p<0.01
Schaefer	Group I: IV iron sucrose Group II: IV iron gluconate	Group I: 29 Group II: 30	250 mg monthly 6 doses	Group A: 11.43 Group B: 11.42 p>0.05

Reviewer's table

The results from three studies (Al-Momen, Yavuz and Hussain) showed statistically significantly higher hemoglobin level in patients who received IV iron sucrose than in those who did not; these results were consistent with the results in pivotal studies. One supportive study (Schaefer) did not show significantly higher hemoglobin in the Venofer group compared to the iron gluconate group.

The sponsor also provided 26 international publications in 1639 dialysis patients to support Venofer use in hemodialysis patients.

Overall, there was substantial evidence to support the Venofer use in treatment of iron deficiency anemia in hemodialysis patients.

The sponsor submitted two studies (Study 50 and 52) to support this indication. Study 50 (Gasche) was a pilot study to evaluate the efficacy of Erythropoietin treatment in addition to Venofer therapy in 40 patients with Crohn's disease associated anemia but not to evaluate the efficacy of Venofer treatment. The study showed a mean increase in hemoglobin of 3.3 g/dl from baseline in iron sucrose treatment alone group. However, the study did not provide evidence of stable baseline hemoglobin and stable Crohn's disease condition to support baseline and end-of-treatment comparison.

Study 52 (Bulvik) was a nonrandomized, open-label, parallel group study of Venofer versus Ferrlecit in 123 patients with iron deficiency anemia who had malabsorption and

intolerance to oral iron. No study protocol was available. The study did not demonstrate superiority of Venofer over Ferrlecit in treatment of iron deficiency anemia and was not specifically designed as an equivalence or non-inferiority trial ($p > 0.05$). The Venofer group had significantly higher hemoglobin and hematocrit than the Ferrlecit group at baseline that may bias the result in favor of Venofer. The study showed a significant increase in hemoglobin from baseline in both treatment groups ($p < 0.001$). However, the study did not provide stable baseline hemoglobin to support baseline and end of treatment comparison.

The study design and the primary efficacy results for these two studies are summarized in the following table:

Study designs and efficacy results in other population

Studies	Study design	# of patients	Venofer received	Study result: Hemoglobin (g/dl)
50 (Gasche)	Group A: EPO + IV iron sucrose Group B: Placebo + IV iron sucrose	40 patients with Crohn's disease Group A: 20 Group B: 20	200 mg 18 doses	Hemoglobin increase ≥ 2 g/dl: Group A: 95% (95%CI: 74-100%) Group B: 75% (95% CI: 51-91%) $p = 0.20$ Mean increase in hemoglobin: Group A: 4.9 g/dl Group B: 3.3 g/dl $p = 0.004$
52 (Bulvik)	Group A: IV iron gluconate Group B: IV iron sucrose	123 patients with iron deficiency anemia Group I: 50 Group II: 71	Group A: 125 mg 10 doses Group B: 100 mg 10 doses	Hemoglobin in final visit: Group A: 11.33 ± 1.48 Group B: 11.75 ± 1.42 $p > 0.05$ Mean increase in hemoglobin: Group A: 3.2 g/dl ($p < 0.001$)* Group B: 3.0 g/dl ($p < 0.001$)*

*final visit vs. baseline

Reviewer's table

The following are major clinical deficiencies in each study:

1) Study 50 (Gasche):

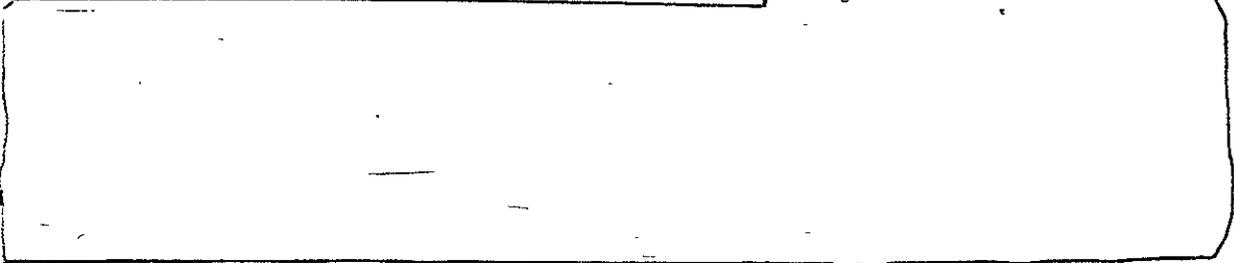
- The study objective was to evaluate the efficacy of EPO treatment in addition to iron hydroxysaccharate therapy in patients with Crohn's associated anemia but was not to evaluate the efficacy of iron sucrose.
- The sponsor did not provide evidence of stable baseline hemoglobin level and stable Crohn's disease condition to support the use of baseline and end of treatment comparison in hemoglobin for iron sucrose treatment.

2) Study 52 (Bulvik):

- The study did not demonstrate superiority of Venofer over Ferrlecit with regard to efficacy. The study was not specifically designed as an equivalence or non-inferiority trial.
- The sponsor did not provide evidence of stable baseline hemoglobin to support baseline and end of treatment comparison.
- The study protocol is not available.
- This was a nonrandomized study.

- The mean baseline hemoglobin levels were not comparable between groups. Patients in Ferrlecit group had statistically significantly lower hemoglobin (8.2 ± 1.3 vs. 8.7 ± 1.1 , $p < 0.01$) and hematocrit (26.1 ± 3.5 vs. 27.4 ± 3.1 , $p = 0.045$) than patients in Venofer group. (bias in favor of Venofer)
- Many patients (44 patients, 36.3%) did not complete the study.

Based on the clinical studies in this NDA submission,



In this NDA submission, only Study 52 enrolled 123 patients with iron deficiency anemia who had malabsorption or intolerance to oral iron. As mentioned above, the study was not an adequate and well-controlled study. An adequate and well-controlled study with strong result to demonstrate efficacy of Venofer treatment

11.2 Overall Safety Assessment:



Two studies are submitted related to this indication. Study LU98002 enrolled 23 hemodialysis patients and Study LU98001 enrolled 10 hemodialysis patients with anaphylactoid reactions to iron dextran. Neither study did provided detailed clinical information, intervention and outcome of anaphylactoid reactions to iron dextran at baseline for study patients to validate these reactions.

In Study LU98002, only 12 patients (52%) of 23 enrolled patients satisfied the inclusion criteria according to the definition of anaphylactoid reaction to iron dextran defined in the study protocol. In addition, some patients enrolled in the study experienced intolerance or anaphylactoid reaction to Venofer treatment. This suggests that patients who have intolerance or anaphylactoid reaction to iron dextran may also have intolerance or anaphylactoid reaction to Venofer.

In Study LU98001, monitoring for anaphylactoid reaction within the first hour of drug administration was not described in study protocol. 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.

Extent of Exposure:

Venofer has been used as an iron sucrose intravenous preparation for 50 years in Switzerland and has been marketed in 35 countries world-wide. About 4099 patients (2416 ESRD patients and 1683 other patients) have received at least one dose of iron sucrose in 74 study reports/publications. Thirteen reports/publications including 1111 ESRD patients and 18 reports/publications including 1151 other patients reported at least one adverse event in their study results. Overall, about 30% patients received 100 mg dosage, 30% received 200 mg dosage, and 5% received 500 mg or greater dosage.

In three pivotal trials, 231 hemodialysis patients received at least one dose of Venofer treatment. All patients received Venofer 100mg in each dialysis session during the treatment. Among 231 patients, 70 (91%) patients in LU98001 and 20 (87%) patients in LU98002 received total 10 Venofer treatment doses, and 111 (85%) patients in VIFOR/001 received the total Venofer treatment dose as scheduled according to baseline hemoglobin and weight. A total of 91 (91%) patients in LU98001 and LU98002 received all Venofer doses as undiluted injection over 5 minutes. The remaining 9 patients in the two trials and all 131 patients in VIFOR/001 received Venofer doses diluted in 100 ml 0.9 sodium chloride infused over approximately 30 minutes. In VIFOR/001 trial, a test dose (50mg in 2.5 ml diluted in 50 ml 0.9 sodium chloride infused over 5-15 minutes) was required for all patients within 2 weeks before the study enrollment.

Common Adverse Events:

About 80% patients reported at least one adverse event during and following the treatment period in 231 patients in three pivotal trials. The common adverse events of Venofer treatment were hypotension (39%), Cramps (27%), nausea (17%), headache (12%), vomiting (9%), chest pain (7%), dizziness (7%), diarrhea (6%), abdominal pain (5%), and hypertension (5%).

Serious Adverse Events:

Overall, 3 patients died in three pivotal trials. The cause of death in one patient was considered due to hypoglycemia reaction or myocardial infarction, one due to coumadin necrosis, and one due to rejection of renal transplant. All deaths were not considered related to study drug by investigator. A total of 42 patients (18%) experienced serious adverse events during the study in three pivotal trials. The most common serious adverse events were pneumonia (3%), vascular access problem (2%), GI bleeding (1%), cellulitis

(1%), pleural effusion (1%), hypoglycemia (1%), chest pain (1%), angina pectoris (1%), sepsis (1%), graft rejection (1%), and accidental injury (1%).

Discontinuations due to adverse events:

A total of 9 patients discontinued Venofer treatment permanently due to adverse events in three pivotal trials. These adverse events were severe diarrhea, graft rejection (2 patients), GI bleeding, neutropenia, tiredness, renal transplant, drop hemoglobin, and nephrectomy site problem. The treatment was discontinued temporarily in 5 patients in LU98001 due to adverse events including severe diarrhea (2 patients), application site reaction, malaise, and fistula repair.

Anaphylactoid reactions:

No life-threatening or serious anaphylactic/anaphylactoid reactions were reported in three pivotal trials. Five patients developed pruritus, urticaria, or rashes after Venofer treatment and were considered as having anaphylactoid reactions (1 in LU98001, 2 in LU98002 and 2 in VIFOR/001). The incidence of anaphylactoid reaction was 3% in patients in LU98001 and LU98002 where the test dose was not given, and 1.5% in VIFOR/001 where a negative test dose was required in study enrollment. Dyspnea and hypotension were not included in the above figure because of lack of detailed clinical information to determine if those were due to underlying disease or anaphylactoid reaction. Overall, no patient discontinued treatment due to above reactions. In 8 published studies, 13 (2.9%) patients reported anaphylactoid reactions during or after the infusion of study drug in 455 hemodialysis patients and these reactions included urticaria/skin discomfort (8), wheezing (2), hypotension (3).

There were much lower incidences of anaphylactoid reaction reported by post-marketing pharmacovigilance data from 11 countries between 1992-1997 (0.017%) and in Vifor's post-marketing safety report between 10/1997 and 8/1999 (0.0055%) using spontaneous report system. Twenty-seven cases of anaphylactic/anaphylactoid reactions were reported in the safety report by Vifor during that period. Eight cases (0.0016%, 6 of them reported between 3/1999 and 8/1999) were serious anaphylactic/anaphylactoid reactions (anaphylactic shock, loss of consciousness, dilated pupil, collapse, dyspnea, hypotension, or convulsion) which had been related to Venofer treatment. There were two fatal cases (cardiac arrest) which occurred in September 1999 following Venofer infusion in India reported in IND submission and one of them had chronic renal failure and anemia. No detailed information is provided. Two deaths and 3 serious cases of necrotizing enterocolitis in pre-term infants in a French study were reported in April 2000 in IND submission. No detailed information about these cases is available at the time of this review.

This reviewer recommends that a warning statement for life-threatening anaphylactic/anaphylactoid reactions be included in the labeling. A Phase IV study with appropriate size to obtain further information regarding anaphylactoid reactions should be conducted.

A recommendation for serum ferritin level monitoring during the treatment should be stated clearly in the label.

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

12. Conclusions and Recommendations

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

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

The major clinical deficiencies are:

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

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

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

The major deficiencies are:

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

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

 / S /[^] 10-13-2000
Min Lu, M.D., M.P.H.

cc:
NDA 21-135 (SEI 033)
HFD-180/Division file
HFD-180/L Talarico
HFD-180/K Robie-Suh
HFD-180/M Lu
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HFD-720/T Permutt
HFD-180/J Choudary
HFD-180/L Zhou
10/13/2000

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Appendix 1: Foreign Market Authorization Status

Table 1: World-wide market authorisation status

Country	Action - Date	Launch Date	Trade Name(s)	Comments / Qualifications
Switzerland	AQ - 2/50 AR/N - 12/94	1950 -	Ferrum Hausmann i.v. Venofer®	Ex. child (<3Y) Repeated test dose Care when lactating
Italy	A - 11/52 AR - 2/86 V - 5/98	1953 - -	Ferrum Hausmann i.v. - -	- Unrelated to safety
Bolivia	A - 1/60 AR - 3/94	1995 -	Ferrum i.v. -	- -
Portugal	A - 11/64 AR/N - 2/91	1965 -	Ferrum Hausmann i.v. Venofer® solucao injectavel i.v.	-
Mexico	A - 6/67 AR/N - 1/94	1968 -	Ferranina Venoferrum solucion injectable	-
Germany	A - 11/69 AT - 8/97 N - 3/98	1970 - 9/99	Ferrum Vitis - Venofer®	- Reg purchased
Cyprus	A - 7/73 AR - 7/98	2/94	Venofer® Ampoules for Intravenous Injection	-
Venezuela	A - 11/73 AR/N - 7/94 AR - 7/99	1974 - -	Intafer intravenoso ampollas Venofer®	-
Brazil	A - 7/79 AR - 11/93	1979 -	Noripurum solucao injectavel endovenoso	- -
Dominican Republic	AR - 2/85 AR - 10/90	1985 -	Ferrum Hausmann injectable i.v.	- -
Argentina	A - 3/85 AR - 7/97	5/85 -	Ferranin injectable intravenoso	- -
Thailand	A - 8/85 N - 97	1986 1997	Ferrum Hausmann i.v. Venofer®	-
Guatemala	A - 2/86 AR - 4/96	1986 -	Ferrum Hausmann i.v. injectable	- -
Hong Kong	A - 6/88 Reg - 11/97	1988 -	Ferrum i.v. injection Venofer®	- -
Taiwan	A - 10/88 AR - 8/94 V - 10/98	10/88 - -	Ferrum Hausmann i.v.	- -
Ecuador	A - 2/89 AR - 5/96 AR - 8/99	6/90 - -	Ferrum Hausmann intravenoso	- -
Greece	A - 3/90 V - 7/98	3/90 -	Ferrum Hausmann i.v.	- Unrelated to safety
Romania	A - 3/93 N - 10/97	5/98	Ferrum Hausmann Venofer®	-
Panama	A - 3/94 AR - 4/99	3/94	Ferrum Hausmann i.v. solucion injectable	-

Table 1: World-wide market authorisation status (continued)

Country	Action - Date	Launch Date	Trade Name(s)	Comments / Qualifications
Peru	A - 1/96	1996	Venofer® i.v. injectable	-
Israel	AQ - 3/96 AR - 4/98	3/96	Venofer®	Monitored drug
Bulgaria	A - 5/96	5/96	Venofer®	-
Turkey	A - 9/96	10/96	Venofer®	-
Lebanon	A - 11/96	1998	Venofer®	-
El Salvador	A - 3/97	1997	Ferrum Hausmann endovenoso	-
Chile	A - 7/97	10/97	Venofer® solución inyectable	-
Columbia	A - 9/97	10/97	Venofer®	-
Netherlands	AQ - 10/97	1997	Venofer®	Indications vary
Sri Lanka	preliminary 12/97 A - 12/98	2/98	Veno Ferrum	-
UK	AQ - 6/98	9/98	Venofer®	Ex. child, pregnancy Indications vary Contraindications vary Dose varies Max. inf rate varies
Saudi Arabia	A - 6/98	6/98	Ferosec ampoules	-
France	A - 12/98	8/99	Venofer®	Ex. pregnancy, Preferably not during lactation Indications vary Max. dose 300 mg Administration only in diluted form as an infusion
India	A - 1/99	1/99	Venofer®	-
Uruguay	A - 3/99	1/99	Venofer	-
Haiti	A*	1980	Ferrum Hausmann i.v.	* Swiss marketing authorisation is valid

Abbreviations: A = authorised; AQ = authorised with qualifications; AR = authorisation renewal; AT = authorisation taken over; Ex = excluded; N = trade name of product changed; Reg = registration; V = voluntary marketing application withdrawal by company; inf = infusion.

Sponsor's table in NDA Vol. 14.1, pp. 5-6

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Appendix 2: Study Schedules

LU98001

Schedule of Evaluations

Procedure	Screening	Observation Period ^a	Treatment Period ^b Days 1-22		End of Treatment Visit ^c	Follow-up Visits ^d
	Days -14 to 0	Days -7 to 0	Day 1	Days 2-22	Day 24	Days 36±2 and 57±2
Informed consent	X					
Inclusion/exclusion criteria	X					
Complete medical history and physical examination; height	X					
Brief physical exam		X	X	X	X	
Vital signs/weight	X	X	X	X	X	
Clinical chemistry tests	X				X	
HIV and HbsAg ^e	X					
ECG ^f	X				X	
Pregnancy test	X					
Serum B12 and folate	X					
Administration of study drug ^g			X	X		
Hematologic parameters ^h	X		X	X	X	X
Clinical chemistry	X				X	
Iron indices ⁱ	X		X		X	X
Concomitant medications	X	X	X	X	X	X ^j
Adverse event assessment		X	X	X	X	X ^k

^a The pretreatment observation period for dialysis-associated adverse events was the period covering the 3 dialysis sessions immediately prior to Day 1 of the study.

^b Study Day 1, day of the first dose of study drug, for all patients occurred on a Wednesday or a Thursday. Patients received iron sucrose injection on Days 1, 3, 6, 8, 10, 13, 15, 17, 20 and 22.

^c End of treatment clinical and laboratory assessments were performed immediately prior to the first dialysis session after completion of iron sucrose injection therapy. For most patients, this occurred on Day 24.

^d The first follow-up assessment occurred 2 weeks after the last dose of iron sucrose injection and the second follow-up assessment occurred 5 weeks after the last dose of iron sucrose injection (ie, 8 weeks after the start of therapy).

^e HbsAg, if not performed within the prior 12 months; HIV test optional.

^f If not performed within 1 month prior to enrollment or if patient had a known history of cardiac disease. Repeated at end of treatment only if clinically warranted.

^g Study drug was completely administered within 30 minutes of the start of dialysis.

^h All hematology parameters were assessed at screening and on Days 1 (baseline), 8, 15, 22, 24, 36, and 57.

ⁱ Iron indices (serum transferrin saturation, serum ferritin, total iron binding capacity, and serum iron) were assessed at screening and on Days 1 (baseline), 24, 36, and 57. All blood samples for laboratory studies were drawn prior to the start of dialysis.

^j Patients were not to receive any changes in r-HuEPO dose, additional iron supplementation or blood transfusions until after the Day 57 evaluation.

^k All adverse events occurring between the end of treatment and the 2-week follow-up visit (Day 36) were to be reported; all serious adverse events occurring between the end of treatment and the 5-week follow-up visit (Day 57) were to be reported.

Sponsor's table in NDA Vol. 14.2, pp. 23

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LU98002

Schedule of Evaluations

Procedure	Screening Days -14 to 0	Observation Period ^a Days -7 to 0	Treatment Visits ^b Days 1-22		End of Treatment Visit ^c Day 24
			Day 1	Days 2-22	
Informed consent	X				
Complete medical history and physical examination; height Brief physical exam	X				
Vital signs/weight	X	X	X	X	X
Clinical chemistry tests	X				X
HIV and HbsAg ^d	X				
ECG ^e	X				X
Pregnancy test	X				
Serum B12 and folate	X				
Administration of study drug ^f			X	X	
Hematologic parameters ^g	X		X	X	X
Iron indices ^h	X		X		X
Concomitant medications	X	X	X	X	X
Adverse event assessment		X	X	X	X

^a The baseline observation period for dialysis-associated adverse events was the period covering the three dialysis sessions immediately prior to Day 1 of the study.

^b Study Day 1 for all patients occurred on a Wednesday or a Thursday. Patients received iron sucrose on Days 1, 3, 6, 8, 10, 13, 15, 17, 20 and 22.

^c End of treatment clinical and laboratory assessments were performed immediately prior to the first dialysis session after completion of iron sucrose therapy. For most patients this occurred on study Day 24.

^d If not performed within the prior 12 months, HIV test optional.

^e If not performed within one month prior to enrollment or if patient had a known history of cardiac disease. Repeated at end of treatment only if clinically warranted.

^f Study drug was completely administered within 60 minutes of the start of dialysis.

^g Hematologic parameters (hemoglobin, hematocrit) were assessed at screening and on Days 1 (baseline), 8, 15, 22, and 24.

^h Iron indices (serum transferrin saturation and serum ferritin) were assessed at screening and on Days 1 (baseline) and 24. All blood samples for laboratory studies were drawn prior to the start of dialysis.

Sponsor's table in NDA Vol. 1.28, pp. 20

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VIFOR/001

Schedule of Evaluations

Procedure	Screening Period (2 Weeks)	Treatment Period (Variable)	End of Treatment Visit ¹	Observation Period (1 Month)
Informed consent	X			
Complete medical history and physical examination; height	X			X
Brief physical exam	X	X	X	X
Vital signs/weight ²	X	X	X	X
HIV, HbsAg ³	X			
ECG ⁴	X			X
Pregnancy test	X			
Administration of study drug ⁵		X		
Hematologic ⁶ parameters	X	X	X	X
Iron indices ⁶	X		X	X
Concomitant Medications	X	X	X	X
Adverse event assessment		X	X	X
Clinical chemistry determinations ⁷	X	X	X	X

Extracted from the original study protocol (see Section 10.1).

¹ If the last Venofer® ampoule was administered during session 1 or 2 of an even week, the same procedures for special investigations and physical examinations relevant for session 3 of that week were followed.

² Blood pressure and heart rate were to be recorded before the start of each dialysis session, 1 hour after the start of dialysis, prior to administration of study drug, and 15 minutes (treatment period only), 1, 2, and 3 hours after the start of administration of study drug. Oral temperature was to be recorded during the treatment period before the start of study drug and at 15 minutes, 1 and 2 hours after the start of study drug.

³ If not previously done.

⁴ If not performed within 1 month or if patient had a known history of cardiac disease. If there was any underlying cardiac pathology, an ECG should have been recorded on the screening day. A post-study ECG was performed to compare with baseline ECG.

⁵ Study drug was to have been administered 1 hour after the start of dialysis. The first injection, a test dose (2.5 mL=50 mg iron) of Venofer® to check for tolerance, was to be administered within 2 weeks following the screening assessments. If no anaphylactoid reaction was observed following the test dose, a full 5 ml dose of Venofer® was to be administered during each subsequent hemodialysis session until the total calculated dose for each patient was administered.

⁶ Hematologic and iron studies were to be performed before the start of each dialysis session at screening, on the day of the Venofer® test dose, and thereafter every 2 weeks for the duration of the study.

⁷ Clinical chemistries were to be determined before the start of each dialysis session on the day of Venofer® test dose administration and thereafter monthly for the duration of the study.

Sponsor's table in NDA Vol. 1.24, pp. 11

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**Appendix 3: Mean changes in hemoglobin from baseline in ITT population
by difference between screening and baseline hemoglobin levels**

LU98001

Baseline minus screening (g/dl)	Screening Mean±SEM*	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
≤ ±0.5	10.3±0.1 (n=51)	10.3±0.1 (n=51)	11.2±0.2 (n=46)	0.99±0.13 (n=46)	11.5±0.2 (n=49)	1.25±0.16 (n=49)	11.3±0.2 (n=47)	1.04±0.20 (n=47)
> 0.5	10.0±0.2 (n=15)	10.9±0.2 (n=15)	11.8±0.4 (n=14)	0.87±0.27 (n=14)	12.3±0.3 (n=13)	1.35±0.29 (n=13)	12.4±0.4 (n=14)	1.36±0.44 (n=14)
<-0.5	9.9±0.4 (n=5)	8.8±0.5 (n=5)	10.4±0.7 (n=4)	1.9±0.81 (n=4)	11.1±0.6 (n=5)	2.28±0.68 (n=5)	10.9±0.2 (n=5)	2.14±0.50 (n=5)
>0	10.2±0.1 (n=39)	10.7±0.1 (n=39)	11.7±0.2 (n=34)	0.95±0.14 (n=34)	12.0±0.2 (n=36)	1.21±0.14 (n=36)	12.1±0.2 (n=36)	1.29±0.20 (n=36)
<0	10.1±0.2 (n=29)	9.7±0.2 (n=29)	10.8±0.2 (n=27)	1.10±0.22 (n=27)	11.2±0.2 (n=28)	1.45±0.27 (n=28)	10.9±0.3 (n=27)	1.23±0.29 (n=27)
=0	10.0±0.2 (n=3)	10.5±0.3 (n=3)	11.5±0.6 (n=3)	1.07±0.28 (n=3)	12.4±0.9 (n=3)	1.97±0.67 (n=3)	10.2±1.6 (n=3)	-0.23±1.59 (n=3)

*SEM: Standard error of the mean

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

LU98002

Hemoglobin Change (Baseline minus screening) (g/dl)	Screening Mean±SEM	Baseline Mean±SEM	End-of-Treatment	
			Visit Mean±SEM	Change Mean±SEM
≤ ±0.5	10.4±0.2 (n=14)	10.5±0.2 (n=14)	11.2±0.3 (n=14)	0.73±0.22 (n=14)
> 0.5	10.1±0.6 (n=2)	10.9±0.4 (n=2)	12.7±0.2 (n=2)	1.75±0.25 (n=2)
< -0.5	10.2±0.1 (n=2)	9.4±0.2 (n=2)	10.7±1.0 (n=4)	1.35±0.85 (n=2)
>0	10.3±0.2 (n=7)	10.8±0.2 (n=7)	11.7±0.4 (n=7)	0.86±0.31 (n=7)
<0	10.3±0.2 (n=9)	9.9±0.3 (n=9)	11.0±0.4 (n=8)	1.01±0.22 (n=8)
=0	10.6±0.4 (n=3)	10.6±0.4 (n=3)	11.4±0.8 (n=3)	0.76±0.95 (n=3)

Reviewer's table based on sponsor's data in NDA Vol. 1.29, pp. 202-209

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VIFOR/001

Hemoglobin Change (baseline minus screening) (g/dl)	Screening Mean±SEM (n)	Baseline Mean±SEM (n)	Observation Week 2		Post-Study	
			Visit Mean±SEM (n)	Change Mean±SEM (n)	Visit Mean±SEM (n)	Change Mean±SEM (n)
≤ ±0.5	7.1±0.2 (n=93)	7.1±0.2 (n=93)	9.2±0.3 (n=47)	1.89±0.18 (n=47)	8.8±0.2 (n=90)	1.65±0.18 (n=90)
> 0.5	6.8±0.3 (n=19)	7.6±0.3 (n=19)	8.7±0.4 (n=12)	1.18±0.21 (n=12)	9.3±0.4 (n=19)	1.74±0.38 (n=19)
< -0.5	7.8±0.3 (n=15)	6.9±0.3 (n=15)	10.2±0.6 (n=9)	3.11±0.71 (n=9)	9.7±0.5 (n=14)	2.89±0.59 (n=14)
>0	6.9±0.2 (n=63)	7.3±0.2 (n=63)	8.9±0.3 (n=34)	1.52±0.21 (n=34)	8.8±0.2 (n=62)	1.55±0.21 (n=62)
<0	7.2±0.2 (n=50)	6.8±0.2 (n=50)	9.7±0.4 (n=27)	2.57±0.29 (n=27)	9.1±0.3 (n=47)	2.24±0.28 (n=47)
=0	8.0±0.5 (n=14)	8.0±0.5 (n=14)	8.9±0.8 (n=7)	1.41±0.19 (n=7)	9.4±0.5 (n=14)	1.44±0.31 (n=14)

Reviewer's table based on the sponsor's data in NDA Vol. 1.22, pp. 164-167

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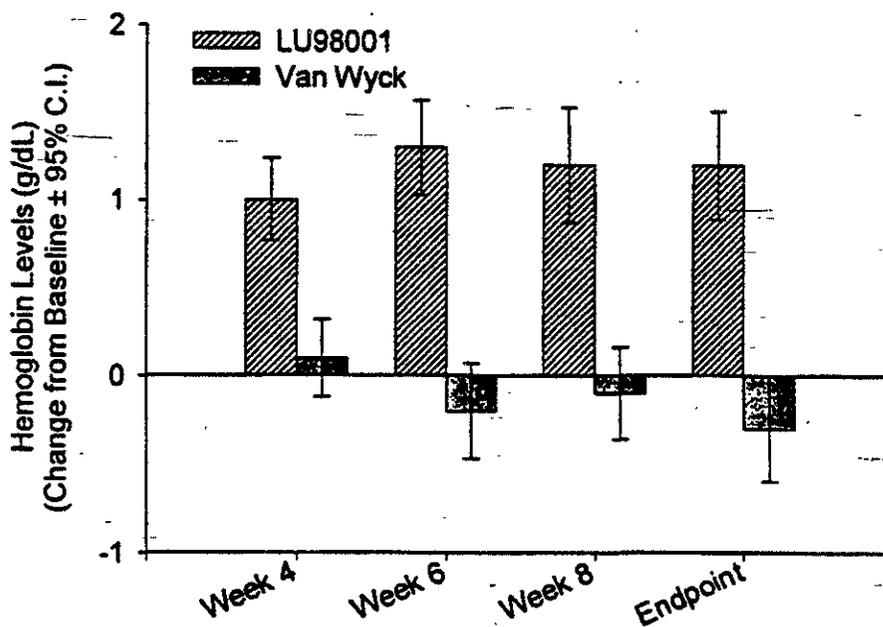
Appendix 4: Comparison between LU98001 and All-Patients in Historical Control

Table 13. Changes from Baseline in Hemoglobin (g/dL) (All-Patients — Van Wyck)

Visit Window	Treatment	N	Baseline Mean (SE)	Visit Mean (SE)	Change Mean (SE)	95 C.I. for Change	p-value
Week 4	LU98001	69	10.3 (0.12)	11.3 (0.15)	1.0 (0.12)	0.77, 1.24	0.0034
	Van Wyck	48	11.1 (0.10)	11.2 (0.11)	0.1 (0.11)	-0.12, 0.32	
Week 6	LU98001	73	10.3 (0.11)	11.6 (0.15)	1.3 (0.14)	1.03, 1.57	0.0001
	Van Wyck	46	11.1 (0.10)	10.8 (0.13)	-0.3 (0.14)	-0.57, -0.03	
Week 8	LU98001	71	10.3 (0.11)	11.5 (0.17)	1.2 (0.17)	0.87, 1.53	0.0011
	Van Wyck	43	11.2 (0.10)	11.1 (0.12)	-0.1 (0.13)	-0.36, 0.16	
Endpoint	LU98001	76	10.3 (0.11)	11.4 (0.17)	1.2 (0.16)	0.89, 1.51	0.0001
	Van Wyck	55	11.1 (0.09)	10.7 (0.14)	-0.3 (0.15)	-0.59, -0.01	

p-values: ANCOVA.

Figure 5. Mean Changes from Baseline in Hemoglobin (g/dL) (All-Patients — Van Wyck)



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Table 15. Hematocrit (%) Changes from Baseline by Visit (All-Patients — Van Wyck)

Visit Window	Treatment	N	Baseline Mean (SE)*	Visit Mean (SE)	Change Mean (SE)	95 C.I. for Changes	p-value
Week 4	LU98001	69	32.1 (0.42)	35.2 (0.51)	3.1 (0.37)	2.36, 3.83	0.0017
	Van Wyck	48	35.5 (0.36)	35.7 (0.36)	0.2 (0.40)	-0.58, 0.98	
Week 6	LU98001	72	32.4 (0.40)	36.0 (0.53)	3.6 (0.44)	2.74, 4.46	0.0001
	Van Wyck	46	35.6 (0.37)	34.8 (0.41)	-0.8 (0.45)	-1.68, 0.08	
Week 8	LU98001	70	32.3 (0.41)	35.6 (0.60)	3.3 (0.54)	2.24, 4.36	0.0118
	Van Wyck	43	35.7 (0.38)	35.7 (0.45)	-0.1 (0.47)	-1.02, 0.82	
Endpoint	LU98001	75	32.3 (0.39)	35.6 (0.58)	3.3 (0.51)	2.30, 4.30	0.0004
	Van Wyck	55	35.3 (0.34)	34.8 (0.53)	-0.5 (0.54)	-1.56, 0.56	

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

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.

Table 17. Ferritin Levels (ng/mL) at Baseline and Endpoint (All-Patients — 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	49	428.2 (39.24)	398.9 (44.09)	-29.3 (21.15)	-70.6, 12.2	

p-values: ANCOVA.

Table 19. Transferrin Saturation (%) at Baseline and Endpoint (All-Patients — 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	0.0009
	Van Wyck	21	28.2 (2.12)	23.9 (1.57)	-4.4 (2.38)	-9.1, 0.3	

p-values: ANCOVA.

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List of References

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**The Safety Update Review is contained within
Clinical Review #1**

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