

Patients who discontinued or decreased study drug due to an adverse event

Patient number	Sex	Age (years)	Adverse event	Relationship to study drug
Discontinuation of study drug				
36	F	23	Graft rejection Drop in Hb	Not related Not related
64	M	26	Graft rejection	Not related
66	M	43	GI bleeding	Not related
103	M	46	Raised lymphocytes Raised eosinophils Reduced neutrophils	Not related
106	M	37	Tiredness Sleepiness	Possible related
118	F	36	Drop in Hb	Not related
119	F	25	Renal transplant	Not related
127	F	40	Nephrectomy site problem	Not related
Decrease of study drug				
69	F	41	Fistula stopped working	Not related
70	M	42	Hypotension	Not related
72	F	25	Back pain Raised GGT	Not related
117	M	61	Hypotension	Not related
129	F	45	Vertigo	Not related
136	M	52	Hematuria	Not related
144	F	45	Hypotension	Possible related
150	F	40	Hypotension	Not related

Reviewer's table based on the sponsor's data in NDA Vol. 1.19, pp. 273-331.

Clinical Laboratory Evaluation:

For clinical chemistry data, missing data at week 4 were replaced by the first available value for any week after week 4; missing data at post-study were replaced by the last available value for any week.

The analyses of clinical chemistry data showed albumin increased significantly (39.7 ± 4.7 vs. 39.0 ± 4.5 g/l, $p=0.02$) in post-study compared to screening and ALT increased in post study but was not statistically significant (17.6 ± 17.7 vs. 15.4 ± 14.1 , $p=0.07$) compared to screening. Other clinical chemistry data, including urea, creatinine, alkaline phosphatase, total bilirubin, GGT, AST, LDH were not significantly changed from screening to post study.

Vital Signs and Physical Examination:

Vital signs (including oral temperature, body weight, systolic and diastolic blood pressure, heart rate) were not significantly changed from screening to post study. The number of abnormalities in all body systems remained unchanged from screening to post-study.

7.1.3.4 Re-Analyzed Report by the Sponsor

The sponsor indicates that because the database for Study VIFOR/001 was not available, the sponsor re-created database using the copies of all original case report forms and re-analyzed the data using the new database.

The primary objectives of re-analysis were:

- To verify the evaluable patient population for efficacy analysis.
- To verify the effect of study drug on hemoglobin, hematocrit, serum ferritin and serum transferrin saturation.
- To verify the safety profile of study drug as defined by adverse events.

The secondary objectives of re-analysis were:

- To determine whether patients reached targeted hemoglobin levels as defined by National Kidney Foundation Dialysis Outcomes Quality Initiative (NKF-DOQI) guidelines with or without erythropoietin (EPO) treatment.
- To re-examine safety data for evidence of anaphylactoid reaction.

7.1.3.4.1 Efficacy Re-analyses

The following analyses were added in efficacy re-analysis:

- Hematocrit as an efficacy parameter
- Modified ITT population that included all patients with at least one post-baseline efficacy assessment in all efficacy analysis.
- The percentage of patients who reached the NKF-DOQI guideline recommendation of a Hemoglobin level ≥ 11 g/dl was summarized for patients who had a hemoglobin level of ≥ 8 g/dl at baseline whether or not they were receiving EPO at baseline.
- An analysis to investigate the effect of EPO use on the changes in hematological variables. The group of patients who were receiving EPO at baseline was compared to the group not receiving EPO using two-sample t-tests.

7.1.3.4.2 Safety Re-analyses

The following analyses were added in safety analysis:

Anaphylactoid reactions:

The case report form data were reviewed for evidence of anaphylactoid reactions. The following events were considered to be suggestive of a potential anaphylactoid reaction:

- Bronchospasm
- Laryngeal edema
- Urticaria
- Angioedema
- Systolic/diastolic blood pressure drop >30 mmHg within 1 hour after a dose of study drug

A medical review of concomitant medication for the treatment of anaphylaxis was performed.

Among patients with dialysis sessions in both the treatment and observation periods, the frequency of blood pressure decreases of >30 mmHg among all dialysis sessions in the treatment period was compared to that among all the dialysis sessions in the observation period. Blood pressure changes were evaluated at 15 minutes and one hour after the administration of study drug during the treatment period and at the second hour of dialysis in the observation period.

7.1.3.4.3. Re-analyzed Efficacy Results

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The mean ratios of the efficacy parameters for observation week 2 and study completion to those at baseline were analyzed by an analysis of variance, using a logarithmic transformation. Ninety-five percent confidence intervals for the ratios were obtained by inverting the confidence intervals for the log ratios. The ANOVA is equivalent to a paired t-test on the log-transformed data.

Verification of Efficacy in the Evaluable Population

The efficacy evaluable patient population of the original report was used for the per protocol efficacy re-analysis.

The mean change of efficacy parameters for the evaluable population is shown below:

Table 3. Mean Hematologic Values for the Efficacy Evaluable Population (n=105)

Variable	Mean at Baseline	Mean at Observation Week 2	Mean Ratio ^a (%)	Mean at Study Completion	Mean Ratio ^b (%)
Hemoglobin (g/dL)	7.2±1.6	9.0±1.9	125****	9.2±1.9	128****
MCV (fL)	90.6±77.4	89.5±7.2	106*	89.9±7.0	106*
MCH (pg)	28.5±17.4	28.9±2.7	106**	29.3±2.7	108***
MCHC (g/dL)	34.9±28.7	32.3±1.8	98.3	32.6±1.7	99.1
Hematocrit (%)	22.5±4.9	27.9±6.0	124****	28.5±6.1	127****
Serum Ferritin (ng/mL)	65.1±48.8	512.7±320.8	969****	440.2±333.8	751****
Total Iron Binding Capacity (pmol/L)	54.4±16.7	42.4±12.4	78.1****	42.8±14.3	78.9****
Serum Transferrin Saturation (%)	11.4±5.4	27.7±10.9	261****	27.6±12.3	254****

Extracted from Section 10.2, Appendix A, Tables 7.1, 8.1, 9.1, 10.1, 11.1 and 12.1.

^a Ratio (%): Log-transformed ratio of observation Week 2 values to baseline values.

^b Ratio (%): Log-transformed ratio of study completion values to baseline values.

*p<0.05

**p<0.010

***p<0.001

****p<0.0001

Sponsor's table in NDA Vol. 1.24, pp. 23

Efficacy results for the efficacy evaluable population in the re-analysis were compared to those from the original study report in the following table.

Table 4. Comparison of Efficacy Analyses for the Efficacy Evaluable Population (n=105)

Variable	Mean at Screening/Baseline		Mean Ratio ^a (%) at Observation Week 2		Mean Ratio ^b (%) at Study Completion	
	Original	Re-analysis	Original	Re-analysis	Original	Re-analysis
Hemoglobin (g/dL)	7.3	7.2	128****	125****	128****	128****
MCV (fL)	83.1	90.6	108****	106*	109****	106*
MCH (pg)	26.9	28.5	109****	106**	109****	108***
MCHC (g/dL)	32.1	34.9	101*	98.3	101	99.1
Hematocrit (%)	22.5	22.5	126****	124****	127****	127****
Serum Ferritin (ng/mL)	68.4	65.1	1059****	969****	837****	751****
Serum Transferrin Saturation (%)	13.2	11.4	226****	261****	219****	254****
Total Iron Binding Capacity (pmol/L)	55.9	54.4 (n=93)	77.9****	78.1**** (n=93)	77.9****	78.9**** (n=93)

Extracted from original report and Section 10.2, Appendix A, Tables 7.1, 8.1, 9.1, 10.1, 11.1, & 12.1.

^a Ratio (%): Log-transformed ratio of observation Week 2 values to baseline values.

^b Ratio (%): Log-transformed ratio of study completion values to baseline values.

*p<0.05

**p<0.010

***p<0.001

****p<0.0001

Sponsor's table in NDA Vol. 1.24, pp. 24

The sponsor indicated that the results based on the re-analysis did not exactly match the results of the efficacy data in the original report. The hematology data match more closely (means differ by about 5% or less) than the data for the iron parameters (means differ by about 10% or more). The sponsor believes that most of the inconsistencies in mean Hb at observation Week 2 appear to result from a value other than the nominal observation Week 2 value being used as the observation Week-2 value in the original report.

Modified ITT population:

All patients with at least one post baseline assessment were included in the modified ITT population. Two patients had no hematology or serum chemistry data after baseline and were excluded from the efficacy analyses for the modified ITT population. The modified ITT population included 130 of 132 patients (98.5%).

Table 5. Mean Hematologic Data for the Modified ITT Population (n=130)

Variable	Mean at Baseline	Mean at Observation Week 2	Mean Ratio ^a (%)	Mean at Study Completion	Mean Ratio ^b (%)
Hemoglobin (g/dL)	7.2±1.6	8.9±1.9	122****	8.9±2.1	124****
MCV (fL)	89.7±69.7	89.0±7.4	105*	89.4±7.7	105**
MCH (pg)	28.3±15.7	28.8±2.7	106**	29.1±2.8	107***
MCHC (g/dL)	34.4±25.8	32.4±1.8	99	32.6±1.7	100
Hematocrit (%)	22.4±4.8	27.4±6.2	122****	27.8±6.4	123****
Serum Ferritin (ng/mL)	72.3±65.2	506.9±328.6	911****	458.6±364.8	693****
Total Iron Binding Capacity (pmol/L)	53.6±15.7	42.5±12.1	79****	43.0±13.6	80****
Serum Transferrin Saturation (%)	11.7±5.5	27.0±11.3	246****	25.8±12.3	227****

Extracted from Section 10.2, Appendix A, Tables 7.2, 8.2, 9.2, 10.2, 11.2, & 12.2.

^a Ratio (%): Log-transformed ratio of observation Week 2 values to baseline values.

^b Ratio (%): Log-transformed ratio of study completion values to baseline values.

*p<0.05

**p<0.010

***p<0.001

****p<0.0001

Sponsor's table in NDA Vol. 1.24, pp. 25

Statistically significant increases in the ratios of Hb, Hct, serum ferritin, total iron binding capacity and serum transferrin saturation were observed at both Week 2 (p<0.0001) and post-study (p<0.0001). Similarly, statistical significant increase in the ratios of MCV (p=0.012 at Week 2 and p=0.008 post-study) and MCH (p<0.0017 at Week 2 and p<0.001 post-study) were observed. No significant changes were observed for MCHC.

Efficacy Analyses for the NKF-DOQI Criterion for Hemoglobin:

Among 35 patients with baseline hemoglobin level ≥ 8 g/dl, 6/12 (50%) patients receiving EPO and 7/13 (30.4%) not receiving EPO met the guideline. The result is summarized in the following table:

Table 6. Efficacy Evaluable Patients with Baseline Hb ≥8 g/dL Meeting the NKF-DOQI Guideline of Hb ≥11 g/dL

Patients ^a on EPO	Patients Who Reached ^b HB ≥11 g/dL		Total # of Patients	Percentage Meeting Guideline
	Yes	No		
Yes	6	6	12	50.0%
No	7	16	23	30.4%
Total	13	22	35	37.1%

Extracted from Section 10.2, Appendix C, Table 4.1.

^a Patients with baseline Hemoglobin values of at least 8 g/dL.

^b Hemoglobin ≥11 g/dL at anytime during the study.

Sponsor's table in NDA Vol. 1.24, pp. 26

Reviewer's Comments:

For ITT population, the result is shown below:

ITT patients with baseline Hb \geq 8 g/dl who reached Hb \geq 11 g/dl
at anytime during the study by EPO status

Patients on EPO	Patients who reached Hb \geq 11 g/dl		Total # of Patients	Percentage Meeting Guideline
	Yes	No		
Yes	6	7	13	46.1%
No	10	18	28	35.7%
Total	16	25	41	39.0%

Reviewer's table based on the sponsor's data in NDA Vol. 1.27, pp.299.

Efficacy Analyses for EPO and Non-EPO Patient Populations:

A total of 21/105 patients (20%) in the efficacy evaluable population and 27/130 patients (21%) in the modified ITT population were receiving EPO at baseline. For both populations, the mean baseline values of Hb, HCT, transferrin saturation, and serum ferritin were higher in patients receiving EPO compared to those not receiving EPO. The EPO and non-EPO groups of the modified ITT population differed significantly at baseline with respect to Hb ($p=0.006$), HCT ($p=0.005$), transferrin saturation ($p<0.001$), and TIBC ($p=0.026$). Both the EPO and non-EPO groups had significant ($p\leq 0.001$) increases in Hb and HCT from baseline, but these values were not significantly different from each other. In the efficacy evaluable and the modified ITT populations, the ratios at Week 2 and at study completion for serum ferritin and serum transferrin saturation were significantly ($p=0.036$) higher for the non-EPO group than for the EPO group.

7.1.3.4.4 Re-analyzed Safety Results

A total of 131 patients were included in the safety analyses, both in the original report and the re-analysis.

Extent of Exposure:

Patients in the modified ITT population received a mean of 14.8 ± 4.63 doses (mean of 1480 mg iron) of Venofer in this study. The sponsor indicated that the Venofer dose reported in the original report could not be validated for two patients. For one patient, the study report listed 17 doses of Venofer, but only 16 doses were identified in the case report form for the re-analysis. For another patient, the study report listed administration of 15 doses, but the re-analysis database listed 16 doses.

Adverse Events:

The COSTART adverse event dictionary was used to map verbatim adverse events to preferred terms and body systems for the re-analysis. In contrast, the original report summarized adverse events by the term reported on the case report form. Adverse events identified only in comments on the case report forms were not included in the re-analysis summaries.

All Adverse Events

In the re-analysis, 115 patients (87.8%) had at least one adverse event irrespective of any relationship to study drug. The most common body systems affected were body as a whole (89 patients; 67.9%), the cardiovascular (76; 58.0%), the digestive (55; 42.0%), the

nervous (22; 16.8%), the hemic and lymphatic (20; 15.3%), the musculoskeletal (14; 10.7%), and the respiratory (16; 12.2%) systems. The most common adverse events were hypotension (51.1%), pain (47.7%), nausea (23.7%), and headache (16.0%). All other adverse events were less frequent (occurring less than 10%). The majority of patients had adverse events considered by the investigator to be mild (44; 33.6%) or moderate (55; 42.0%); 16 patients (12.2%) experienced adverse events that were considered to be severe. The only severe adverse events that were reported in more than one patient were hypotension (4/131, 3.1%), hypertension (3/131, 2.3%), and GI hemorrhage (2/131, 1.5%).

Treatment-Related Adverse Events

In the treatment period, 111/131 patients (85%) had at least one adverse event, irrespective of relationship to study drug, in the original report, compared with 110/131 patients (84%) in the re-analysis. In the original report, the most common adverse event during the treatment period was hypotension (61 patients; 47%), followed by cramps (which were coded as pain in the re-analysis) (48 patients; 37%) and nausea (31 patients, 24%). The re-analysis also reported hypotension (57 patients; 44%) as the most frequent adverse event, followed by pain (46 patients; 35%) and nausea (29 patients; 22%). Comparison of the drug-related adverse events also showed similar results. The most common drug-related adverse event during the treatment period was hypotension in the both original report (17 patients, 13%) and the re-analysis (16 patients; 12%), followed by nausea (4 patients, 3%, in both).

In the re-analysis, 28 patients (21.4%) had "related" adverse events during treatment period. None of these related events were considered to be severe. The body systems most commonly affected were the cardiovascular system (17 patients; 13.0%), the digestive system (8 patients; 6.1%), and the body as a whole (6 patients; 4.6%). The most common "related" event was hypotension (16 patients; 12.2%), followed by nausea (4 patients; 3.1%).

The following table compares drug related adverse event from re-analysis to original study report:

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Table 7. Comparison of Original Report and Re-analysis for Incidence of Drug Related Adverse Events During the Treatment Period

Body System Preferred Term	Number of Patients with Related Adverse Events During the Treatment Period Original Report	Number of Patients with Related Adverse Events During the Treatment Period Re-analysis
Body as a Whole		
Abdominal Cramps	1	0
Abdominal Pain		1
Abscess	1	1
Back Pain		1
Musculoskeletal Pain	1	
Chest Pain	1	2
Tight Chest	1	
Lab Test Abnormal		1
Acute Presbycusis	1	
Pain		1
Cramps	1	0
Sleepiness	1	0
Tiredness	1	0
Respiratory System		
Pneumonia	2	1
Skin and Appendages		
Rash	1	1
Pruritus	1	1
Cardiovascular System		
Hypertension	1	1
Hypotension	17	16
Digestive System		
Liver Function Tests Abnormal	2	2
Nausea	4	4
Vomiting	2	1
Nausea and Vomiting		1
Hemic and Lymphatic System		
Polycythemia		1
Special Senses		
Deafness		1

Extracted from original report and Section 10.2 Appendix A, Table 4.4.

Bold numbers indicate differences in the number of adverse events for each term in the re-analysis database compared with the original report.

Sponsor's table in NDA Vol. 1.24, pp. 29

The sponsor indicated that most of the differences between the original report and the re-analysis (5 patients with a total of 7 adverse events in the original report) arose due to mapping of adverse events to a dictionary preferred term in the re-analysis report compared with the verbatim term summarized in the original report. In addition, two patients had adverse events in the re-analysis summary which were not in the original report summary (Patient No 0005000152: hematocrit increased mapped to lab test abnormal and increased erythrocytes mapped to polycythemia; Patient No. 0004000109: nausea); one patient mistakenly had no adverse events entered into the re-analysis database, but had three events in the original report (Patient No. 0004000106: tiredness, sleepiness, hypotension); and, one patient (Patient No. 0001000006) had pneumonia with a missing relationship to study drug that was counted as related in the original report whereas it was entered as not related in the re-analysis database.

Discontinuation or Dose Reduction due to Adverse Events:

In the re-analysis, 5 patients were prematurely discontinued from the study due to an

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adverse event. The sponsor indicated that although two additional patients had adverse events which caused discontinuation of study medication, the reasons for withdrawal from the study were withdrawal of consent and renal transplant. Another patient (Patient 0003000052) had a clotting A-V fistula which was the reason for discontinuation from the study after 13 doses, however, study medication was not checked as "discontinued" for this adverse event on the adverse event case report form.

The patients discontinued due to an adverse event are shown below:

Table 8. List of Patients Who Discontinued Treatment Due to an Adverse Event

Patient ID	Sex (M/F)	Age (yrs)	Adverse Event ^a	Intensity	Event Date		Relationship to treatment
					Onset	Stop	
0001000036	23	F	Graft rejection	Severe	10/30/95	11/21/95	Not related
			Drop in hemoglobin	Mild	10/30/95	11/02/95	Not related
0004000064	26	M	Graft rejection	Moderate	11/01/95	11/13/95	Not related
0004000066	43	M	Gastrointestinal bleeding	Severe	11/29/95	11/30/95	Not related
0004000106 ^c	37	M	Tiredness and sleepiness	Moderate	10/05/94	10/06/94	Possible
0004000118	36	F	Drop in hemoglobin	Moderate	12/23/94	b	Not related
0004000119 ^d	25	F	Renal transplant	b	12/29/94	b	Not related
0004000127	40	F	Nephrectomy site problems	Moderate	03/08/95	03/15/95	Not related

^a Except for patient 0004000119 whose outcome data were not available and patient 0001000036 who died but whose date of death was unknown, none of these events resulted in permanent disability or death. Patient 0004000103, 46 year-old male, had AEs of increased lymphocytes and eosinophils and reduced neutrophils, these events were considered of moderate severity, not related to study drug, and were indicated as cause for discontinuation (start date 09/16/94 - unavailable); the dosing record did not confirm this and the patient's status was indicated as completed study.

^b Data not available.

^c Reason for discontinuation was consent withdrawn.

^d Reason for withdrawal was renal transplant.

Note: All discontinuations due to an adverse event listed in this table were verified against the original report data listings.

Sponsor's table in NDA Vol. 1.24, pp. 30

In the re-analysis report, the sponsor indicated that no patients had their dose of Venofer reduced due to an adverse event.

Reviewer's Comment: In original data listing, 8 patients discontinued study drug and 8 patients decreased study drug due to an adverse event (see original study results in "Discontinuations and Decrease of Study Drug Due to Adverse Events" section).

Death and Other Serious Adverse Events:

Death:

In the re-analysis report, the sponsor indicated that one patient died following rejection of a renal transplant after removal from the study. The sponsor's narratives for this patient is shown below (All dates and days are derive from the case report forms):

Patient 0001000036: This 23-year-old mixed race female had a medical history of chronic

renal failure on hemodialysis, anemia, and two failed renal transplants (25 January 1990 and 03 May 1995).

She received IV Venofer (100 mg iron/day on dialysis) from 04 October 1995 (Study Day 1) to 30 October 1995 (Study Day 12). On Study Day 12, the patient had an acute graft rejection, and developed a worsened hypochromic anemia (baseline hemoglobin, 5.5 g/dL; Study Day 12, 5.0 g/dL) and mild hypoproteinemia (baseline albumin, 35 g/L; Study Day 12, 27 g/L). The graft rejection was life threatening and considered a serious adverse event. That same day, the patient was hospitalized and discontinued from the study because of the graft rejection and the decrease in her hemoglobin value. At the time of discontinuation, the patient had received a total of 12 doses of 100 mg each of the study drug. On 02 November 1995, the hypochromic anemia was resolved when the patient received a blood transfusion, and on 21 November 1995, the graft rejection was considered resolved, however; at the end of the study, the hypoproteinemia was ongoing (albumin, 29 g/l, on 02 November 1995, Study Day 13). The Patient was reported to have died, but the date of this event was not reported. During the study, the patient took dietary supplements and medicine for hypertension (amlodipine, atenolol), for hyperphosphatemia (aluminum hydroxide) and for nausea and vomiting while on dialysis.

The investigator considered the graft rejection, hypoproteinemia, and the hypochromic anemia unrelated to the study drug.

The sponsor did not provide the case report form for above patient.

Other Serious Adverse Events:

In the re-analysis, 20 patients are listed as having experienced serious adverse events. These included 4 additional patients who were hospitalized, but not indicated as a serious event in the original study report. Five of these patients were also discontinued from the study.

The following is the sponsor's table:

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Table 9. List of Patients Who Experienced A Serious Adverse Event

Patient ID	Sex (M/F)	Age (yrs)	Adverse Event ^a	Study Period	Intensity	Relationship to Treatment	Event Date		Study Medication Changed?
							Onset	Stop	
0001000004	M	30	Vascular access problems	Observation	b	Possible	10/01/94	b	No
0001000007	M	45	Cellulitis	Treatment	Moderate	Not related	11/14/94	b	No
			Severe pleural effusion & tuberculosis	Observation	Moderate	Possible	12/28/94	b	No
			Pneumonia	Treatment	Moderate	b	11/30/94	12/06/94	No
0001000012	M	38	Hypoglycemia	Observation	Severe	Not related	02/03/95	02/03/95	No
0001000014	F	25	Salpingo-oophoritis	Treatment	Severe	Not related	02/16/95	02/24/95	No
0001000015	M	27	Pneumonia	Treatment	Moderate	Possible	02/03/95	b	No
0001000016 ^c	M	57	Chest pain	Treatment	Moderate	Not related	02/13/95	02/13/95	No
0001000020	M	38	Pneumonia	Observation	Moderate	Possible	05/03/95	05/10/95	No
0001000021	M	39	Uveitis	Treatment	Severe	Not related	04/30/95	06/05/95	No
0001000031	M	53	Gastro-intestinal bleeding	Observation	Severe	Not related	11/03/95	11/03/95	No
			Hypotension	Observation	Severe	Not related	11/03/95	11/03/95	No
0001000036	F	23	Graft rejection	Treatment	Severe	Not related	10/30/95	11/21/95	Discontinued
0002000203	M	62	Pneumonia	Observation	Severe	Not related	06/10/95	06/13/95	No
0004000062	F	41	Hernia repair	Treatment	Mild	Not related	12/03/95	12/10/95	No
0004000064	M	26	Graft rejection	Treatment	Moderate	Not related	11/01/95	11/13/95	Discontinued
0004000066	M	43	Gastrointestinal bleeding	Treatment	Severe	Not related	11/29/95	11/30/95	Discontinued
0004000105 ^c	M	39	Chest pain & cramps	Treatment	Severe	Not related	09/23/94	9/23/94	No
0004000118	F	36	Hemiparesis	Treatment	Moderate	Not related	12/12/94	b	No
0004000119 ^c	F	25	Renal transplant	Treatment	b	Not related	12/29/94	b	Discontinued
0004000127 ^c	F	40	Nephrectomy site problems	Treatment	Moderate	Not related	03/08/95	03/15/95	Discontinued
0004000131	M	38	Dyspnea, fever & pneumonia	Treatment	Moderate	Not related	04/05/95	04/08/95	No
0004000144	F	45	Endophthalmitis	Treatment	Severe	Not related	10/23/95	11/04/95	No

a: Patient 0004000118 experienced an event which resulted in permanent disability; patient 0001000036 experienced an event which resulted in immediate risk of death; event outcome was unknown for patients 0004000066 & 0004000127.

b: Data not available.

c: Patients were hospitalized, but the event was not indicated as serious.

Note: All serious adverse events listed in this table were verified against the original data listings.

Sponsor's table in NDA Vol. 1.24, pp. 31

Anaphylactoid Reactions:

In the re-analysis report, the following events were considered to be suggestive of a potential anaphylactoid reaction: bronchospasm, laryngeal edema, urticaria, angioedema, or systolic/diastolic blood pressure drop >30 mmHg within 1 hour after a dose of study drug.

A summary of the signs and symptoms of potential anaphylactoid reactions is shown below:

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Table 10. Summary of Signs and Symptoms of Potential Anaphylactoid Reactions

Event	Incidence
Bronchospasm ^a	0 (0%)
Laryngeal Edema	0 (0%)
Urticaria ^b	1 (0.8%)
Angioedema	0 (0%)

Extracted from Section 10.2, Appendix A, Table 16.

^a While no bronchospasm was reported, two patients reported bronchitis and six reported coughing.

^b Patient 0002000204 reported generalized rash considered by the investigator as possibly related to study drug.

Note: In addition, Patient 0003000051 reported an allergic reaction considered by the investigator to be mild and not related to study drug.

Sponsor's table in NDA Vol. 1.24, pp. 42

One patient developed urticaria considered by the investigator as possibly related to study drug. The sponsor indicated that the one occurrence of "urticaria" was not accompanied by any decrease in blood pressure and therefore, not an anaphylactoid reaction. The sponsor indicated that no cases of bronchospasm, asthma, or other respiratory distress and no episodes of laryngeal or angioedema were reported. No patients received medication for an anaphylactoid reaction, such as bronchodilators or epinephrine.

Reviewer's Comment: According to the sponsor's definition of anaphylactoid reaction, urticaria alone should be considered as anaphylactoid reaction. Also, one patient reported pruritus on Day 34 and was considered related to Venofer treatment by the investigator. These two cases should be considered as anaphylactoid reactions. One patient reported mild pruritus on Day 1 and one reported dyspnea on Day 32 were considered not related to study drug by the investigator.

In the sponsor's re-analysis, 71 (54.6%) of all patients (130) had a decrease in systolic blood pressure (SBP) of >30 mmHg and 15 (11.5%) had a decrease in diastolic blood pressure within 1 hour of study drug dose.

The sponsor indicated that dialysis with acetate (only 23 of 131 patients were dialyzed with bicarbonate) is known to cause significant decreases in blood pressure and no attempt was made to estimate the clinical impact of such a decrease. For example, patients who dropped from 200 mmHg SBP to 170 mmHg SBP were not differentiated from those who dropped from 130 mmHg SBP to 100 mmHg SBP.

To identify a potential drug effect compared with an effect of dialysis, the 105 patients with dialysis sessions in both the treatment and observation periods were evaluated for decreases of >30 mmHg in systolic blood pressure. Among these 105 patients, decreases were observed only during the treatment period (i.e., at 15 minutes and/or 1 hour following study drug administration, i.e., during the second hour of dialysis) in 29 (30%) patients, only during the observation period (at the second hour of dialysis) in 10 (10%) patients, and during both periods in 31 (30%) patients.

In a further attempt to determine whether the changes of >30 mmHg in systolic blood pressure occurred more frequently during the treatment period, the incidence of these

decreases was determined among all dialysis sessions during the treatment period and among all dialysis sessions during the observation period for the 105 patients with dialysis sessions in both periods. The proportion of sessions with systolic blood pressure decreases of >30 mmHg was 7.3% for the treatment period and 6.0% for the observation period. These results are summarized in the following table:

Table 11. Summary of >30 mmHg Decreases in Systolic Blood Pressure by Dialysis Sessions

Study Period	Average Number of Dialysis Sessions ^a	Average Percentage of Sessions ^a with a Decrease in SBP of >30 mmHg
Treatment	16.4	7.3%
Observation	10.9	6.0%

Extracted from Section 10.2, Appendix C, Table 3.1.

^a For 105 patients with dialysis sessions during both the treatment and observation periods.

Sponsor's table in NDA Vol. 1.24, pp. 43

Clinical Laboratory Evaluations:

The change from baseline to treatment Week 4, observation Week 2 and post-study was calculated and analyzed using a paired t-test.

For the hematological tests, the changes from baseline were statistically significantly different from zero at both observation Week 2 and post-study for erythrocytes (increased) and platelets (decreased)(the original report found statistical significance for erythrocytes only). Statistically significant changes from baseline at observation Week 2 were detected for basophils and reticulocytes (statistical significance for safety population was not determined in the original report).

For the serum chemistry tests, statistically significant changes from baseline to post study were detected for GGT and albumin (statistical significance for safety population was not determined in the original report).

The changes in platelets, basophils, albumin, and GGT were minimal and of no clinical significance.

Vital Signs:

Heart rate, blood pressure, oral temperature, and body weight are summarized at baseline and post-study for both the efficacy evaluable population and the safety population. No data are available for treatment Week 4. The mean change in baseline to post-study was calculated and analyzed for the efficacy evaluable population using a paired t-test. None of the mean changes from baseline were statistically significantly different from zero or of clinical importance. These results are similar to those in the original report.

7.1.3.5 Reviewer's Comments

7.1.3.5.1 Efficacy Assessment

Study VIFOR/001 showed a significant increase in hemoglobin from baseline after Venofer treatment at 2 week follow-up and 4 week post-study (p=0.0001). Hematocrit,

serum ferritin, and transferrin saturation also increased significantly at 2 week follow-up and post-study ($p=0.0001$) from baseline. The study results were consistent with LU98001. The treatment effect was 1.7 ± 0.17 g/dl increase in mean hemoglobin after a mean of 1.5 g iron given as Venofer injection. Similar to study LU98002, this study was limited by only two baseline hemoglobin values available in this baseline-controlled study. However, the overall results support Venofer use for hemodialysis associated iron deficiency anemia.

7.1.3.5.2 Safety Assessment

In this study, 131 patients were included in the safety analysis. One patient died more than 3 weeks after removal from the study due to renal transplant-rejection. Sixteen patients were reported as having a total of 21 SAEs during the study. The most common SAEs were pneumonia (5 patients), GI bleeding (2 patients) and graft rejection (2 patients). Eight patients discontinued study drug and 8 patients decreased study drug due to an adverse event. Graft rejection (2 patients) was the most common event in patients who discontinued study drug and hypotension (4 patients) was the most common event in patients who decreased study drug. The most common adverse events during the study were hypotension (53%), cramps (44%), nausea (27%) headache (16%), vomiting (14%) and chest pain (10%). For anaphylactoid reactions, two patients experienced urticaria or pruritus considered related to Venofer treatment by the investigators. Of 130 patients who were analyzed, 71 (54.6%) patients had a decrease in systolic blood pressure (SBP) of >30 mmHg and 15 (11.5%) had a decrease in diastolic blood pressure within 1 hour of study drug dose.

7.2 Supportive Clinical Efficacy Trials

7.2.1 Trial 1: Study Al-Momen (Vol. 1.30)

Study Protocol

The study protocol is not available.

7.2.1.1 Study Report

Title of the Study: Enhancement of rHuEPO Effect By Iron(III)-Hydroxide Sucrose Complex In Hemodialysis Patients.

Study Investigator: Abdul-Kareem Al-Momen, MB, College of Medicine & King Khalid University Hospital, Riyadh, Saudi Arabia.

Study Period: 1994-1996

Study Objectives: The aim of this study was to investigate the efficacy of iron(III)-hydroxide sucrose complex supplementation in hemodialysis patients on rHuEPO therapy and with normal iron stores.

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Study Design: This was a single center, open-label, nonrandomized, no-treatment concurrent controlled study. Enrolled patients were allocated to two treatment groups according to patient own choice:

Group A: iron (III)-hydroxide sucrose complex (VENOFER®) 100 mg intravenously weekly.

Group B: no iron treatment.

In both groups, patients received rHuEPO at dose of 50 U/kg intravenously 3 times a week. The rHuEPO dose was increased by 25 U/kg every 4 weeks in poor responders. Total treatment duration was 12 weeks.

Study Population: 123 patients participated in the study, 53 in group A, 70 in group B. **Inclusion criteria:** hemodialysis patients with end stage renal disease, age >15 years, normal baseline iron stores (serum iron >10 µg/l, total iron binding capacity (TIBC) <70 µmol/l, serum ferritin >50 µg/l), normal baseline serum folate and vitamin B12 levels, normochromic, normocytic anemia (Hb <9 g/dl, normal MCV, MCH, MCHC) and reticulocytopenia (reticulocytic count <0.1 of RBC), and informed consent obtained. **Exclusion criteria:** iron, folate or B12 deficiencies, hemolytic anemia, bleeding tendency, advanced cardiac and/or hepatic disease, systemic inflammatory disease (e.g. SLE), cancer or infection, pregnancy or breast-feeding.

Study Drug: Iron(III)-hydroxide sucrose complex (VENOFER®, which is sold in Saudi Arabia as Ferosac, SPIMACO, Saudi Arabia) was given 100 mg iron as intravenous injection once a week for total 12 weeks. The commercial packs were used.

Erythropoietin (rHuEPO, Eprex®, Janssen-Cilag AG) as started at 50 U/kg 3 times a week. This dose was increased by 25 U/kg every 4 weeks in poor responders. The commercial packs were used.

The sponsor did not provide definition of "poor responders".

Study Plan: Screening visit included pre-selection, medical history, check of eligibility, physical examination, obtaining patient's oral informed consent. Eligible patients were allocated to either rHuEPO with IV iron or rHuEPO without IV iron group according to patients' choice. Follow up visits included efficacy and safety assessment, blood sample collection, possible dose adaptations of rHuEPO, body weight, blood pressure, heart rate, and laboratory tests including complete blood count, reticulocytes, iron, TIBC, and serum ferritin. Final visit included repeated blood sample collection, assessment of efficacy and safety and global assessment of efficacy by the physician. The duration of the study was 12 weeks. The sponsor did not provide the time of follow-up visit.

Efficacy Parameters: These included hemoglobin, hematocrit, erythrocyte count, serum ferritin, serum iron, TIBC, rHuEPO dose, and time to target hemoglobin.

Safety Assessment: All adverse events (AEs), including non-serious and serious AE (SAEs), were to be recorded on a standard form at each visit, along with the description of the event, the dates of its beginning and end, its frequency and intensity, and its outcome. Vital signs, laboratory tests, assessment of adverse events were also to be recorded at each scheduled visit.

Statistical Methods: The sponsor indicated that sample size was determined arbitrarily and the initial aim was to recruit at least 50 patients in each arm. Patients were allocated either to group A or B, according to their choice. Mann-Whitney test was used to compare between two groups for efficacy parameters. Wilcoxon test was used to compare between different visits in the same group for efficacy parameters. The sponsor did not provide the rationale to use these two nonparametric tests.

7.2.1.2 Study Results

Disposition of Patients: A total of 123 patients participated in the study. Four patients (1 in group A and 3 in group B) were withdrawn prematurely from the study due to the following reasons: kidney transplant (1 patient in group A at week 5), moved to another city (3 patients in group B at week 2, 6, 7, respectively).

Demographic and Baseline Characteristics: The demographic and baseline information in the two groups of patients is shown in the table below:

Table 1: Demographic data at screening (mean \pm SD)

	Group A i.v. iron(III)-hydroxide sucrose complex + rHuEPO	Group B rHuEPO
Age (years)	54.4 \pm 15.3	49.9 \pm 12.2
Sex (M/F)	23/27 3 unknown	24/44 2 unknown
Body Mass Index (kg/m ²)	26.0 \pm 4.7	26.8 \pm 5.6
Systolic Blood Pressure (mmHg)	149.6 \pm 10.7	146.4 \pm 14.7
Diastolic Blood Pressure (mmHg)	81.7 \pm 10.5	80.7 \pm 10.0
On Haemodialysis for (days)	408.9 \pm 295.8	496.4 \pm 269.9

Sponsor's table in NDA-Vol. 1.30, pp. 9

Underlying causes of renal diseases in patients are shown below:

Underlying causes of renal diseases

Concomitant diseases	Group A	Group B
Diabetes mellitus	17	25
Hypertension	4	5
Glomerulonephritis	11	14
Tubulo interstitial nephritis	4	6
Congenital nephritis	0	1
Unknown	17	19
Total	53	70

Reviewer's table based on the sponsor's data in NDA Vol. 1.30, pp. 9

The mean dosage of rHuEPO was 147.4 U/kg in group A and 150 U/kg in Group B per week at enrollment. The sponsor did not provide the duration of rHuEPO treatment.

Efficacy Results:

The efficacy parameters in the two groups at baseline, follow-ups, and final visit are shown below:

Table 2: Comparison of haematological parameters (mean±SD)

	Group A i.v. iron(III)-hydroxide sucrose complex				Group B without iron			
	baseline	follow up 1	follow up 2	final visit	baseline	follow up 1	follow up 2	final visit
Haemoglobin (g/dl)	7.81±0.9	11.05±1.58	12.03±0.91	12.67±0.84 ●●●	7.64±1.09	9.66±1.30 ●●●	11.09±1.05 ●●●	11.98±0.56 ●●●
Haematocrit (%)	23.3±2.8	33.6±5.9	35.8±3.5	37.7±1.0 ●●●	23.7±2.7	29.6±3.6 ●●●	33.0±2.9 ●●●	35.7±1.4 ●●●
Erythrocytes (10 ⁶ /ml)	2.68±0.29	3.73±0.45	4.07±0.40	4.35±0.16 ●●●	2.50±0.37 **	3.08±0.43 ●●●	3.94±0.09 ●●●	3.81±0.24 ●●●
Serum Ferritin (µg/ml)	72.8±11.2	84.8±17.4	101.0±28.6	120.1±39.7 ●●●	60.8±16.3 ●●●	60.1±14.9 ●●●	63.7±26.5 ●●●	60.6±16.4 ●●●
Iron (mmol/l)	13.5±1.3	20.2±11.3	21.5±3.8	25.0±4.5 ●●●	14.3±2.5	14.6±2.5 ●●●	15.0±5.8 ●●●	14.5±2.3 ●●●
TIBC (µmol/l)	57.6±6.9	59.3±8.1	61.6±8.6	62.9±9.6 ●●●	62.6±5.2 ●●●	62.4±6.1 ●●●	61.4±8.6	63.9±4.6

- * p<0.05 vs group I
- p<0.05 baseline vs. final visit
- ** p<0.01 vs group I
- p<0.01 baseline vs. final visit
- *** p<0.001 vs group I
- p<0.001 baseline vs. final visit

Sponsor's table in NDA Vol. 1.30, pp. 10

The mean hemoglobin, hematocrit levels increased statistically (p<0.001) significantly from baseline in both group A and group B patients. The comparison between groups at the final visit, shows statistically significantly higher values for hemoglobin, hematocrit and erythrocytes in group A than in group B (p<0.001). The mean difference between the two groups at final visit was 0.67 g/dl for hemoglobin, 2% for hematocrit, and 0.54 10⁶/ml for erythrocytes.

Serum ferritin, iron and TIBC values in group A were also statistically significantly higher at the final visit compared to baseline (p<0.001), whereas no significant difference could be seen in these parameters between the final visit and baseline in group B. Serum ferritin and iron values at the final visit were higher in group A than group B (p<0.001).

Reviewer's Comments:

Serum ferritin was statistically significantly higher ($p < 0.001$), and TIBC was significantly lower ($p < 0.001$) in group A (Venofer) than group B (without iron) at baseline. All these differences at baseline may bias the results in favor of Venofer treatment.

The mean rHuEPO dose increased in both groups between baseline and the final visit. Comparison between groups at the final visit shows statistically significantly higher rHuEPO doses in group B than group A ($p < 0.001$). The results are shown in following table:

Table 3: Comparison of rHuEPO doses (mean±SD)

	Group A i.v. iron(III)-hydroxide sucrose complex				Group B without iron			
	baseline	follow up 1	follow up 2	final visit	baseline	follow up 1	follow up 2	final visit
Change in rHuEPO dose due to lab results (increased / decreased / no)	NA	13/0/40	2/0/50	0/0/52	NA	54/0/16	25/0/43	0/0/67
Units of rHuEPO since last visit (U/kg/week)	NA	160.7±81.7	179.5±48.3	180.0±52.2	NA	149.1±20.7	206.6±47.3 **	238.5±73.0 ***

- * $p < 0.05$ vs group A
- ** $p < 0.01$ vs group A
- *** $p < 0.001$ vs group A

Sponsor's table in NDA Vol. 1.30, pp. 9

The sponsor indicated that target hemoglobin in group A (iron(III)-hydroxide sucrose complex) was achieved in all patients (mean number of days to reach the target value: 58.4 ± 33.1). In group B 45/67 patients reached target hemoglobin values within 76.8 ± 28.0 days. Comparison between groups showed a statistically significant difference ($p < 0.001$). However, the sponsor did not provide the definition of "target hemoglobin" in the study report.

Safety Assessment:

The sponsor indicated that no serious or non-serious adverse events were observed in connection with the intravenous iron administration or in relation with the rHuEPO treatment. No adverse events were recorded in the sponsor's data listing. However, data were not available for discontinuation of treatment in 52 of 53 patients in group A indicated in the data listing (based on sponsor's data in NDA vol. 1.30, pp. 123).

7.2.1.3 Reviewer's Comments

Study Al-Momen showed significantly increased hemoglobin and hematocrit at end of study as compared to baseline in both groups. However, there was a significantly higher hemoglobin at the final visit in patients treated with iron (III)-hydroxide sucrose than in those without iron treatment ($p < 0.001$). Hematocrit, serum ferritin level and iron level

were also significantly ($p < 0.001$) higher at final visit in treatment group than without treatment group. This study was limited by its nonrandomized design and incompatible between groups in serum ferritin level at baseline. However, the study results support the overall findings in pivotal study LU98001. No adverse event was recorded for the 12-week study.

7.2.2 Trial 2: Study Yavuz (Vol. 1.30)

Study Protocol

The study protocol is not available.

7.2.2.1 Study Report

Title of the Study: Treatment of Iron Deficient Patients on Hemodialysis with I.V. Iron(III)-Hydroxide Sucrose Complex and rHuEPO Simultaneously.

Study Investigator: Mahmut Yavuz, MB, Uludag University, Bursa, Turkey

Study Period: 6/1997-12/1997

Study Objectives: The study objective was to investigate the efficacy and safety of intravenous iron(III)-hydroxide sucrose complex (VENOFER®) in combination with rHuEPO and the influence of intravenous iron on the rHuEPO dose in anemic hemodialysis patients.

Study Design: This was a single center, open-label, nonrandomized, no-treatment concurrent controlled study. Two groups of patients were included in the study: iron deficient (Group I) and non-iron deficient patients (group II). All patients were given 50 U/kg rHuEPO twice or three times per week post dialysis session. Patients in group I were additionally given I.V. iron(III)-hydroxide sucrose complex (VENOFER®), whereas the patients in group II received no further treatment. Duration of the study was 24 weeks.

Study Population: A total of 30 patients participated in the study including 17 patients in Group I and 13 patients in Group II. Inclusion criteria were patients with end stage renal disease on hemodialysis, age between 16 and 70 years, transferrin saturation $< 15\%$ and ferritin < 100 ng/ml for Group I, transferrin saturation $> 15\%$ and ferritin > 100 ng/ml for Group II, normal baseline serum folate and vitamin B₁₂ levels, normochromic, normocytic anemia (Hb < 9 g/dl, normal MCV, MCH, MCHC), and oral informed consent. Exclusion criteria were hemolytic anemia, bleeding tendency, advanced cardiac and/or hepatic disease, systemic inflammatory disease (e.g. SLE), cancer or infection, pregnancy or breast-feeding, or non-compliance.

Study Drug:

Patients in Group I received a test dose of 25 mg Fe(III) as I.V. iron(III)-hydroxide sucrose complex (VENOFER®). If no reaction was observed, 100 mg

Fe(III) as I.V. iron in 100 ml 0.9% sodium chloride was infused for 30 minutes after each hemodialysis together with the rHuEPO, three times weekly for a month. The treatment was continued on a weekly, fortnightly or monthly basis, according to serum ferritin levels.

Patients in both groups were given 50 U/kg rHuEPO (Eprex®, _____), subcutaneously, twice or three times weekly post dialysis session. The dose was altered monthly in order to achieve target hematocrit values (30-32%).

Hemodialysis was applied to the patients by means of _____ dialysers for 4 hours, twice or three times a week. Patients with renal osteodystrophy were also included in the study. Dietary habits and other medical treatments were not changed.

Iron(III)-hydroxide sucrose complex (VENOFER®, _____) and rHuEPO (Eprex®, _____) were administered in an open manner and commercial packs were used. Group II patients did not receive any iron supplementation.

Study Plan: After screening and enrollment, patients had an assessment after 12 weeks and the final visit after 24 weeks. The duration of the study was 24 weeks.

Efficacy Parameters: Hemoglobin, hematocrit, red blood cell count, serum iron, serum ferritin, TIBC, rHuEPO dose, pre-treatment and post-treatment hemoglobin, hematocrit, erythrocytes, serum iron, TIBC and ferritin were assessed at each visit.

Safety Assessment: Any serious and non-serious adverse events experienced by the patient, laboratory tests were recorded at each visit. All adverse events (AE), including non-serious and serious AE (SAE), were documented, along with the description of the event, the dates of its beginning and end, its frequency and intensity, and its outcome. Vital signs were also recorded at each scheduled visit.

Statistical Methods: Mann-Whitney test was used to compare the two treatment groups for efficacy parameters. Wilcoxon test was used to compare between different visits in the same group for efficacy parameters. The sponsor did not provide sample size estimation.

7.2.2.2 Study Results:

Disposition of Patients: A total of 30 patients participated in the study. One patient in group II was lost to follow-up after 12 weeks.

Demographic and Baseline Characteristics:

The mean (\pm SD) amount of days on dialysis was 1975.4 \pm 1328.6 days in group I and 2055.9 \pm 1370.9 days in group II. A total of 9 patients received 2 dialyses per week and 21 patients 3 times per week. The demographics and baseline information are shown below:

Demographic and baseline characteristics in the two-groups

	Group I 17 patients	Group II 13 patients
Age (years)	42.1±17.3	29.6±10.8
Sex (M/F)	7/10	6/6, 1 unknown
Body Mass Index (kg/m ²)	23.4±5.4	19.5±2.9
Systolic Blood Pressure (mmHg)	121.2±9.1	116.2±13.3
Diastolic Blood Pressure (mmHg)	74.4±10.1	65.4±10.5
Renal disease (degree III/IV)	0/17	0/13
On hemodialysis for (days)	1975.4±1328.6	2055.9±1370.9
Number of dialysis per week (2x / 3x)	4 / 13	9 / 21

Sponsor's table in NDA Vol. 1.30, pp. 315

In group I, 5 patients suffered from hypertension and 1 patient had coronary artery disease. Two patients in group II had a neurogenic bladder and 1 suffered from hypotension.

The mean dosage of rHuEPO was 144.1 U/kg in group I and 150 U/kg in Group II per week at enrollment. The sponsor did not provide the duration of rHuEPO treatment.

Some laboratory values that were totally out of range [at baseline: ferritin (2 patients), iron (7 patients); at 12 weeks: ferritin (3 patients), iron (4 patients); and at 24 weeks: iron (4 patients)] were considered as errors and were not included in the evaluation.

Efficacy Results:

A statistically significant increase was observed in the mean hemoglobin, hematocrit and erythrocyte in both groups after 24 weeks compared to baseline. Hemoglobin (p=0.017), hematocrit (p=0.012) and erythrocyte (p=0.015) after 24 weeks were statistically significantly higher in Venofer treatment group (I) than in without Venofer treatment group (II). The results are shown below:

Table 2: Comparison of haematological parameters

	Group I			Group II		
	Baseline	12 weeks	24 weeks	Baseline	12 weeks	24 weeks
Haemoglobin (g/dl)	6.14±1.43	10.29±2.26	11.30±1.72 ***	6.85±1.27	8.70±1.94	9.18±2.16 **
Haematocrit (%)	18.88±4.93	31.68±7.20	35.82±5.75 ***	19.7±3.95	26.45±5.70	28.73±6.64 **
Erythrocytes (10 ⁶ /mm ³)	2.39±0.68	3.63±0.82	3.65±0.57 ***	2.28±0.47	3.02±0.59	3.07±0.58 **
Serum Ferritin (µg/ml)	55.8±85.9	342.7±147.0	428.2±118.5 ***	127.3±130.1	174.6±193.2	325.5±323.4 ns
Iron (mmol/l)	33.1±21.0	53.7±18.6	56.8±30.5 *	98.3±73.9	56.1±17.2	48.1±10.5 ns
TIBC (µg/ml)	425.2±65.4	305.1±48.9	293.1±37.8 ***	402.8±152.9	342.2±51.8	318.7±35.7 ns

* p<0.05 baseline vs. 24 weeks
** p<0.01 baseline vs. 24 weeks
*** p<0.001 baseline vs. 24 weeks
ns not significant

Sponsor's table in NDA Vol. 1.30, pp. 316

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In group I patients, a statistically significant increase in serum ferritin ($p < 0.001$) and iron ($p < 0.05$) at 24 week from baseline and a significant decrease in TIBC ($p < 0.001$) were observed. The changes in group II were not significant for these parameters. While the differences between iron values at baseline were significant ($p = 0.0024$), the differences between iron metabolism parameters at 24 weeks between groups were not statistically significant.

MCV and MCH at baseline were statistically significantly lower in group I than in group II. After 12 and 24 weeks MCV and MCH in group I were statistically significantly higher than at baseline. There was no significant difference in these parameters between the groups after 12 and 24 weeks.

In group I a statistically significant decrease was observed in the rHuEPO dose after 24 weeks. There was a non-significant increase in the rHuEPO dose in group II. There was no significant difference in the rHuEPO dose between the groups at baseline or after 12 weeks, but a significant difference was observed after 24 weeks between the groups.

Table 3: Comparison of rHuEPO doses:

	Group I			Group II		
	Baseline	12 weeks	24 weeks	Baseline	12 weeks	24 weeks
rHuEPO dose (IU/kg/week)	144.1±16.6	136.5±30.6	113.2±39.9	130.8±25.3	148.5±39.8	148.5±39.8
Change of rHuEPO dose due to lab results (decrease / no change / increase)	NA	12/4/1	11/6/0	NA	1/7/5	0/13/0

Sponsor's table in NDA Vol. 1.30, pp. 316

Safety Assessment:

IV iron treatment data was not available in 16/17 patients in group I at 12-week visit (based on data in NDA Vol. 1.30, pp. 366, 455-456). The sponsor indicated that no adverse events were reported during the 24 weeks of the study. Data on discontinuation of the treatment were not available in any patient in group I.

7.2.2.3 Reviewer's Comments

Study Yavuz showed a significantly higher hemoglobin at 24 weeks in patients treated with Venofer than in those without ($p = 0.0167$). Hematocrit was also higher in treatment group ($p = 0.012$) at 24 weeks. Serum ferritin and iron levels were increased significantly at 24 weeks ($p < 0.05$) from baseline. This study was limited by its nonrandomized design and incompatible population in terms of iron store (per inclusion criteria) at baseline between groups. However, the overall study results supported the findings in pivotal trials. No adverse event was recorded for the 24-week study.

7.2.3 Trial 3: Study Hussain (Vol. 1.31)

7.2.3.1 Study Protocol

Title of the Study: Experience of Iron Saccharate Supplementation in Hemodialysis Patients Treated with Erythropoietin.

Study Investigators: Rizwan Hussain, MBBS, The Kidney Center, Karachi, Pakistan

Study Period: 3/1996-6/1996

Study Objective: The study objective was to compare the hemoglobin response, the iron status and erythropoietin requirement between oral and intravenous iron in patients on maintenance hemodialysis.

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

Study Population: Inclusion criteria were patients with renal anemia starting EPO therapy on maintenance hemodialysis, hemoglobin < 8.5g/dl, normal B₁₂, folate level, serum ferritin between 100 - 800 ng/ml, no other cause for anemia (i.e. SLE, rheumatoid arthritis, myeloma, blood loss, etc.), absence of infection, malignancy or surgery in last 3 months, adequate blood pressure control prior to treatment $\geq 140/90$ mmHg, no evidence of severe hyperparathyroidism (PTH <200 pg/ml) and written informed consent. Exclusion criteria were severe liver disease or psychiatric disorder, clinical suspicion of iron overload, serum ferritin <100 ng/ml or >800 ng/ml, active peptic ulcer disease, or known hypersensitivity to intravenous iron products.

Study Drug: Eligible patients were assigned to one of the two treatment groups in 1: 1 ratio.

Group I: Iron-hydroxide-sucrose complex (INJ. VENOFERRUM), 100 mg of iron diluted in 100ml of 0.9% NaCl infused during 15 to 30 minutes twice weekly post dialysis.

Group II: Iron sulfate tablets: 200 mg three times a day.

All patients were treated with a starting dose of 25 U/kg body weight subcutaneously twice weekly. This dose was to be maintained for at least 4 weeks until hemoglobin increased to 12 g/dl. If this target level was exceeded at any stage of study then dose of EPO was to be reduced by one half. If there was no significant rise in hemoglobin concentration (<1 gm/dl) by 4 weeks onward, then the dose of EPO was to be doubled.

Study Plan: The sponsor's event schedule of study is shown below:

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	INITIAL SCREENING	WEEKS 4,8	WEEK 12
<i>Informed consent</i>	✓		
<i>Medical History</i>	✓		
<i>Physical Examination</i>	✓		
<i>Stool (Parasite)</i>	✓		
<i>Hemoglobin</i>	✓	✓	✓
<i>PCV</i>	✓	✓	✓
<i>TLC</i>	✓		✓
<i>Platelet</i>	✓		✓
<i>Reticulocyte%</i>	✓	✓	✓
<i>Transferrin Saturation</i>	✓	✓	✓
<i>Ferritin</i>	✓	✓	✓
<i>PTH</i>	✓		
<i>UREA</i>	✓		✓
<i>Creatinine</i>	✓	✓	✓
<i>Albumin</i>	✓	✓	✓
<i>Alk Phosphatase</i>	✓	✓	✓
<i>B12</i>	✓		
<i>Folic acid.</i>	✓		

Sponsor's chart in NDA Vol. 1.31, pp. 8

Efficacy Parameter: The protocol did not include the plan.

Safety Assessment: The protocol did not include the plan.

Statistical Methods: Descriptive statistics included median, mean and standard deviation for the pre-treatment and post-treatment values as well as pre-post differences. At least 20 dialysis patients with renal anemia were to be studied for a period of 12 weeks. The sponsor did not provide sample size estimation rationale. The sponsor did not provide statistical test to be used in the study.

7.2.3.2 Study Results

Disposition of Patients:

A total of 20 patients participated in the study (10 in each treatment group). Iron therapy was discontinued in 2 patients in group I (IV iron-hydroxide-sucrose complex) before the end of the trial, due to a rise in transferrin saturation (>70%) and serum ferritin (>800 ng/ml).

Demographic and Baseline Characteristics:

The demographic and baseline characteristics are shown below:

Table 1: Demographic data (mean ±SD)

	Group I i.v. iron(III)-hydroxide sucrose complex + rHuEPO	Group II oral iron + rHuEPO
Age (years)	57.8±9.3	52.3±14.6
Sex (M/F)	6/4	7/3
Body Mass Index (kg/m ²)	22.3±3.4	21.6±4.2
Systolic Blood Pressure (mmHg)	131.7±10.5	128.5±11.1
Diastolic Blood Pressure (mmHg)	80.6±6.9	77.5±5.9
Creatinine Clearance (ml/min)	7.56±3.21	6.33±2.40
On Haemodialysis for (days)	549.4±611.3	408.1±524.2

Sponsor's table in NDA Vol. 1.31, pp. 11

The causes of chronic renal failure are summarized in the following table:
Causes of chronic renal failure in patients

Causes for chronic renal failure	Group I	Group II
Chronic glomerulonephritis	4	3
Hypertensive nephropathy	4	1
Diabetic nephropathy	2	6

Reviewer's table based on the sponsor's data in NDA Vol. 1.31, pp. 11

All patients had 2 dialyses per week and none of them were hospitalized.

Efficacy Results:

Mann-Whitney test was used to compare between two groups. Wilcoxon test was used to compare between different visits in the same group. Efficacy variables included hemoglobin, ferritin, transferrin saturation and rHuEPO doses.

The mean hemoglobin increased statistically significantly from baseline to final visit in both groups ($p < 0.01$). At final visit, the mean hemoglobin was statistically significantly higher in the IV iron-hydroxide-sucrose complex group than that in the oral iron group ($p < 0.05$). The mean difference was 1.0 g/dl in hemoglobin between the groups at final visit. The mean rHuEPO dose at final visit was statistically significantly higher in oral iron group than that in IV iron-hydroxide-sucrose complex group.

The results are shown in the following tables:

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Table 2: Comparison of haematological parameters (mean±SD)

	Group I i.v. iron(III)-hydroxide sucrose complex				Group II oral iron			
	baseline	4 weeks	8 weeks	final visit	baseline	4 weeks	8 weeks	final visit
Haemoglobin (g/dl)	7.8±0.2	9.2±0.3	10.4±0.8	11.6±0.7 ●●	8.1±0.3	8.8±0.6	9.8±1.0	10.6±1.2 ●●
Transferrin Saturation (%)	35.6±5.3	35.2±7.0	42.4±19.3	41.7±15.3	38.7±11.9	33.9±9.7	32.0±10.1	29.2±11.6 ●
Serum Ferritin (ng/ml)	413.1±205.4	351±202.0	452±221.2	621.7±278.3 ●●	433.5±261.1	383.5±238.5	382.0±238.6	366.9±230.7 ●
Serum Creatinine (µmol/l)	19.0±7.5	10.1±2.3	9.7±1.7	11.2±2.3	8.3±2.4	8.2±1.7	8.6±2.0	8.7±2.0

- * p<0.05 vs group I
- p<0.05 baseline vs. final visit
- ** p<0.01 vs group I
- p<0.01 baseline vs. final visit

Table 3: Comparison of rHuEPO doses (mean±SD)

	Group I i.v. iron(III)-hydroxide sucrose complex				Group II oral iron			
	baseline	4 weeks	8 weeks	final visit	baseline	4 weeks	8 weeks	final visit
Change in rHuEPO dose since previous visit due to lab results (increase/decrease/no change)	NA	0/0/10	2/0/3	0/1/9	NA	4/0/6	3/0/7	3/0/7
Mean of rHuEPO dose since prev. visit (U/kg/week)	NA	41.1±2.9	41.1±2.9	50.8±17.5	NA	43.8±7.9	63.0±21.0	73.6±17.4 ●

- * p<0.05 vs group I
- p<0.05 baseline vs. final visit

Sponsor's table in NDA Vol. 1.30, pp. 12

Target hemoglobin (11- 12 g/dl) was achieved in all except one patient in group I (IV iron(III)-hydroxide sucrose complex) and the mean number of days to reach target value was 83.3±10.6 days. The target hemoglobin was not achieved in 5 of the 10 patients in group II (oral iron) and the mean number of days to reach target value was 87.8±0.5 days.

Safety Assessment:

Sponsor indicated that no adverse events were observed in connection with the intravenous iron administration or with the rHuEPO treatment. No adverse events were recorded in the data listing.

7.2.3.3 Reviewer's Comments

Study Hussain showed a significantly higher hemoglobin level at final visit in Venofer-treated patients than in oral iron-treated patients (p<0.05). Serum ferritin level and