CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020955

MEDICAL REVIEW(S)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA:	20-995 MAY - 7 1998
Sponsor:	R & D Laboratories, Inc.
Drug:	Ferrlecit®(Ferric Sodium Gluconate) Injection
Class:	Hematinic
Indication:	Iron Deficiency Anemia in Hemodialysis Patients
Date of submission:	12/30/97
Amendments:	12/30/97, 1/7/98, 2/5/98, 2/6/98, 3/9/98, 4/15/98, 4/17/98
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Medical Reviewer:	Kurt Sizer, M.D.

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Introduction

The majority of patients with chronic renal failure have a normocytic, normochromic anemia, due primarily to insufficient production of erythropoietin. Other contributing factors include iron deficiency due to blood loss from repeated laboratory testing, blood retention in the dialyzer and tubing, or gastrointestinal bleeding; severe hyperparathyroidism; aluminum toxicity; folate deficiency; acute and chronic inflammatory disease; shortened red blood cell survival; hypothyroidism; and underlying hemoglobinopathies.

If left untreated, anemia associated with chronic renal failure results in decreased tissue oxygen delivery and utilization, increased cardiac output, cardiac enlargement, ventricular hypertrophy, angina, congestive heart failure, decreased mental acuity, growth retardation in pediatric patients, and overall decreased survival.

Clinical practice guidelines for the treatment of anemia of chronic renal failure were recently published by the National Kidney Foundation (Amer J Kid Dis 1997 30 S194-S240). Information from this guideline is summarized below.

An anemia work-up should be initiated in patients with chronic renal failure when the Hct is <33% (Hb <11g/dL) in premenopausal females and pre-pubertal patients, or; Hct is <37% (Hb < 12g/dL) in adult males and post-menopausal females. Evaluation of anemia should consist of measurement of at least the following: Hct, Hb, RBC indices, reticulocyte count, serum iron, total iron binding capacity, percent transferrin saturation (TSAT), serum ferritin, and a test for occult blood in stool. If no cause of anemia other than chronic renal failure is found, and the serum creatinine is ≥2 mg/dL, anemia is most likely due to EPO deficiency, and EPO therapy should be initiated. Ninety-six percent of patients will respond to EPO at a dose of 450 units/kg/week i.v. (or 300 units/kg/week s.c.) within 4 to 6 months, provided that there are adequate iron stores.

The target range for the Hct should be 33%(Hb 11g/dL) to 36%(Hb 12g/dL). To achieve and maintain this target Hct/Hb, sufficient iron should be administered to maintain a TSAT of ≥20%, and a serum ferritin of ≥100 ng/mL. Oral iron is unlikely to maintain adequate iron stores in EPO-treated hemodialysis patients, so that i.v. iron should be employed. One hundred mg of i.v. iron should be administered for 10 consecutive dialysis sessions. If the TSAT remains at <20%, and/or the serum ferritin remains at <100ng/mL, another course of 100 mg of i.v. iron should be administered every week for 10 weeks. It is anticipated that the required maintenance dose of i.v. iron will vary from 25 to 100 mg/week.

Chronic renal failure patients are unlikely to respond with a further increase in Hct/Hb and/or a further reduction in EPO dose if the TSAT increases to ≥50% and/or the serum ferritin level increases to ≥800 ng/mL.

Normal body iron stores are 800 to 1200 mg. If the initial Hct is 25%, and the target Hct is 35%, the amount of i.v. iron required by the chronic renal dialysis patient on EPO is approximately 1000 mg during the first 3 months. Of this 1000 mg of iron, 400 mg are needed to replace iron losses due to hemodialysis, and approximately 600 mg are needed to support erythropoiesis. Once the target Hct/Hb is achieved, approximately 400 to 500 mg of iron will be required every 3 months, to maintain adequate iron stores.

Note that absolute iron deficiency in chronic renal failure patients has been defined as a TSAT level <20%, and serum ferritin level <100 ng/mL. In contrast, functional iron deficiency results when there is a need for a greater amount of iron to support hemoglobin synthesis, than can be released from iron stores in reticuloendothelial cells. As a result, the TSAT decreases to levels consistent with iron deficiency, while the serum ferritin value remains within the normal (or elevated) range.

Distinguishing between functional iron deficiency and anemia due to chronic disease (with its attendant inflammatory/iron block) is a common clinical problem in patients with chronic renal disease, as the TSAT may be <20%, and serum ferritin may be 100-700 ng/mL in both situations. If it is not clear which of these conditions exists, it is recommended that 50-100 mg of weekly i.v. iron be administered for up to 10 doses. If no erythropoietic response occurs, an inflammatory block is most likely, and no further iron should be given until the inflammatory condition has resolved.

In children, mean daily intestinal blood losses (pre-dialysis) are 6 ml/m2 BSA. Once hemodialysis begins, mean daily intestinal blood loss increases to 11 ml/m2, and dialysis-associated blood loss is approximately 8 ml/m2 per session. Cumulative annual iron losses are therefore approximately 1.6 g/1.73m2 in pediatric hemodialysis patients, and 0.9 g/1.73m2 in pre-dialysis pediatric patients.

The direct administration of iron into the circulation requires a formulation that prevents the toxicity of iron salts. Serum ferritin sequesters iron as a nontoxic, nonionic, ferric oxyhydroxide (FeOOH). Iron is stabilized and solubilized in ferritin as a core of up to 4,000 iron particles surrounded by apoferritin protein monomers. Most parenteral forms of iron are similar to ferritin in chemical structure.

Iron dextran is the only approved form of parenteral iron in the United States. Like ferritin, iron dextran is composed of a core of iron in the ferric state complexed to oxyhydroxide (i.e. FeOOH). This ferric oxide core is surrounded by dextran, which forms a non-covalently bonded, polysaccharide shell around it. Following intravenous injection, iron dextran is removed from plasma by macrophages of the reticuloendothelial system(RES), with a plasma half-life of 6 hours to 3 days. Serum ferritin levels rise within 2 weeks, following intracellular processing and release of iron from the RES.

The primary side effects associated with the use of iron dextran are allergic/anaphylactic reactions. The nature and incidence of this reaction for both iron dextran and iron gluconate, are discussed in the Integrated Summary of Safety section of this review.

Ferrlecit® Injection has been used since 1959 in over 20 countries outside the United States for the intravenous administration of iron to patients with iron deficiency anemia. Currently, the principal intravenous usage is among the 48,000 hemodialysis patients in Germany.

Ferrlecit(sodium ferric gluconate complex in sucrose) is a stable macromolecular complex with an approximate molecular weight of 350,000 daltons. It consists of mono- and di-nuclear iron(III) oxide hydrates which are directly and covalently bonded to saccharates, in a ratio of 2 iron centers to 5 saccharates. In addition, the caroxylate group of gluconate is believed to bridge iron centers with saccharate molecules.

Human pharmacokinetic studies have not been performed with Ferrlecit Injection. In *in vitro* experiments, less than 1% of the iron from Ferrlecit Injection was dialyzable through membranes with pore sizes of 12,000 to 14,000 daltons, over a period of up to 4.5 hours. No preclinical safety concerns were found for the proposed recommended doses in humans.

Two sponsor-conducted studies were submitted by the sponsor on 12/20/97 to support the approval of Ferrlecit as **"first line treatment for iron deficiency anemia in renal hemodialysis patients on supplemental recombinant human erythropoietin"**: studies 5600-01 and 5600-03. Study 5600-01 was a 3-center, randomized, open-label, historically-controlled, comparative study of a high- and low-dose i.v. Ferrlecit regimen, in 108 iron-deficient chronic hemodialysis patients. Study 5600-03 was a single-center, non-randomized, open-label, variable-dose,

compassionate-use, historically-controlled study of the use of i.v. Ferrlecit in 63 iron-deficient chronic hemodialysis patients. Additional studies, including 252 Ferrlecit-treated patients from the published literature, and postmarketing information from Europe, were also submitted to support the safety and efficacy of Ferrlecit in hemodialysis patients.

STUDY 5600-01

Study Protocol

Study 5600-01 was a 3-center, randomized, open-label, historically-controlled, study of the safety and efficacy of 500 mg and 1000 mg of Ferrlecit® in iron-deficient hemodialysis patients. The study period was from 8/2/95 to 3/23/96.

Inclusion criteria were:

- age greater than 18 years
- ferritin level below 200 ng/mL or iron saturation below 18%
- hemoglobin below 10 g/dL or hematocrit below 30%
- patients who have received greater than 90 days of hemodialysis

Exclusion criteria were:

- patients with unstable/uncontrolled pulmonary, cardiovascular, hepatic, endocrine, neurologic, psychiatric, infectious, allergic, immunologic, or malignant disorders
- HIV and/or hepatitis B Surface Antigen positivity
- women who are pregnant, or of child-bearing potential
- use of parenteral iron and/or investigational drugs which may interfere with iron metabolism
- EPO requirement of ≥ 10,000 units t.i.w.

Patients with a known allergy to iron dextran were not excluded from this study.

There was a low and high dose drug regimen. The low dose regimen was 62.5 mg in 50 ml of normal saline, given intravenously over 30 minutes during hemodialysis. The high dose regimen was 125 mg in 100 ml of normal saline, given intravenously over 60 minutes during hemodialysis. Patients were to receive a total of 8 doses of study medication over 8

sequential dialysis sessions (or a period of 16 to 17 days), toward the end of the dialysis session. A 25 mg test dose was administered on Day -5.

Primary and secondary efficacy variables were not defined in the study protocol, but were addressed in the analysis plan. The primary efficacy variable was the change in hemoglobin from baseline to endpoint (last available observation through Day 40). Secondary efficacy variables were changes in hematocrit, percent iron saturation, serum ferritin, serum iron, and mean corpuscular hemoglobin(MCH), mean corpuscular volume(MCV), and mean corpuscular hemoglobin concentration(MCHC) indices.

The study schedule ~~is reproduced below~~ (vol. 16, p. 81):

	Study Day (Treatment Day)												
	-14 to -7	-5 (test dose)	1 (1)	3 (2)	5 (3)	8 (4)	10 (5)	12 (6)	15 (7)	17 (8)	19	33*	47*
Informed Consent	x												
Randomize			x										
HIV, hepatitis, pregnancy tests	x												
Hematology@	x										x	x	x
Hepatic/Renal Labs $	x										x		
P.E./History	x										x		
P.E. (Brief)**			x	x	x	x	x	x	x	x			
ARs		x	x	x	x	x	x	x	x	x	x		
EPO Dosage		x	x	x	x	x	x	x	x	x	x		

* 2 weeks after treatment.
\+ 1 month after treatment.
@ Hematology tests: Hemoglobin, hematocrit, MCV, MCH, MCHC, serum iron, % iron saturation, serum ferritin, WBC count, differential, and platelet count.
$ Hepatic/renal Chemistry tests: ALT, AST, bilirubin, alkaline phosphatase, BUN, creatinine, and glucose.
** Brief physical exam: Blood pressure, pulse, respiratory rate, temperature, chest, heart, lung, abdomen, neurological, skin, and other.

Parenteral iron products and blood transfusions were not allowed during the 2 months preceding study initiation, or during the study. EPO therapy was limited to ≤ 10,000 units t.i.w. Patients receiving Ferrlecit® did not receive oral iron during the study; the historical control population did not receive parenteral iron.

Data sets used for statistical analyses were not prospectively defined in the study protocol or the analysis plan. The intent-to-treat data set consisted of all patients for whom baseline and endpoint data were available. The per-protocol data set consisted of the intent-to-treat data, excluding 29 patients who did not complete the study as per protocol. Twenty-two of these patients required changes in their EPO dose during the study, 5 discontinued the study, and 3 did not meet the inclusion/exclusion criteria. The stable-EPO data set consisted of all patients from the intent-to-treat data set whose EPO dose did not change during the study.

The sample size was determined as reproduced below (vol. 16, p. 90).

A preliminary evaluation of results in previous studies, suggest that a sample of 15 patients per drug level group may be sufficient with a significance level of 0.05 and a power of 0.90. These numbers are based on expected small differences in among-patient baseline ferritin levels, and large changes from baseline in these levels. This sample size is also consistent with expected changes in hemoglobin.

The selection of the doses of Ferrlecit® was determined as described below (vol. 16, p. 84).

The doses of 500 mg and 1000 mg, in 8 divided doses of 62.5 mg and 125 mg, respectively, were selected based on data in published literature, clinical experience with other iron supplementation products used in the United States, average calculated iron losses of 280 mg per month in the dialyzed patient, and the approved labeling on dosage and administration for Ferrlecit in foreign countries where it has been marketed since the 1950s. In general, iron deficiency anemia of the degree found in the entered patient population is usually corrected by the administration of 1000 mg of iron.

Protocol Amendments

The original protocol for study 5600-01 was dated 5/15/95.

Amendment No. 1 was dated 6/9/95, and changed the inclusion criteria of a ferritin level below 200 ng/mL or iron saturation below 18%, to a ferritin level below 100 ng/mL or iron saturation below 18%.

Amendment No. 2, dated 9/15/95, changed the Ferrlecit® diluent from normal saline vials to Baxter normal saline bags. The inclusion criteria of hemoglobin below 10 g/dL or hematocrit below 30%, were changed to a hemoglobin below 10 g/dL or hematocrit at or below 32%.

Amendment No. 3, dated 12/4/95, included the following additions to the study protocol:

Patients who require additional iron supplementation after they have completed the eight treatments and follow up through day 47, may be given subsequent courses of Ferrlecit (eight treatments per course) and be followed as for the first eight treatments. Patients must meet the inclusion/exclusion criteria described in section 2.0. Each subsequent course will be recorded on the Case Report Form and included in the analysis for this study.

Patients randomized to (the low dose regimen) for the initial eight treatments and who continue with additional treatments after day 47 follow up, may receive (the high dose regimen), depending on the response and toxicity experienced during the first eight treatments, at the investigator's discretion. Patients randomized to (the high dose regimen) will continue with the same dose if they continue.

Amendment No. 4 was dated 12/13/95, and changed the exclusion criterion of patients who require ≥ 10,000 units t.i.w. of EPO, to patients who require > 10,000 units t.i.w. of EPO.

Historical Control

The historical control population consisted of 25 chronic hemodialysis patients associated with the University of Colorado Health Sciences Center. Due to drug unavailability beginning in 4/91, intravenous iron dextran was discontinued in these patients for 14 months. All patients were to have stable EPO doses and hematocrit values for at least 2 months prior to iron dextran discontinuation, however the sponsor reports that "many of the patients received blood transfusions before the beginning of the study" (vol. 16, p. 2). All patients received oral iron supplementation throughout the study, although dose and patient compliance were not monitored.

Results are shown below (vol. 16, p. 10):

Effect of Discontinuing Intravenous Iron Dextran in Historical Control Patients

Parameter	Hct	Fe	TIBC	SAT	EPO Dose	Ferritin
Month	(%)	µg/dl	µg/ml	(%)	Units	ng/ml
0	31±4	51±22	223±53	25±14	2732±1167	671±379
1	32±4	58±37	207±51#	28±17	2878±1099	
2	32±3	47±28	219±47	22±14	2829±1243	683±370
3	31±4	44±22	207±34*	22±14	2837±1282	
4	31±4	45±23	219±49	21±11	2900±1236	
5	31±3	50±23	224±47	23±11	2825±1258	667±363
6	32±4	46±20	223±45	21±9*	2887±1293	
7	31±4	45±18	235±70	21±8*	3000±1203	
8	30±3	45±30	235±55	25±30	3112±1200*	568±406#
9	30±3	45±18	235±55*	20±9*	3083±1244*	
10	32±4	46±19	235±54*	20±8#	3261±1482#	
11	31±4	44±35	226±53	19±12*	3321±1464#	516±403#
12	31±3	48±22	218±57	22±9	3392±1487#	
13	31±3	26±19	230±53	21±9*	3333±1373#	
14	31±3	47±27	248±58#	17±9#	3325±1288#	587±670

Results expressed as mean ± SD. * $p < 0.05$, # $p < 0.01$ vs month 0. The number of determinations was at least 40 (range 40-44) at each time point for all measurements.

Hematocrit and serum iron values remained stable throughout the observation period. (Note that the mean iron value of 26 µg/dL at 13 months is likely an editorial error, as the corresponding transferrin saturation of 21% and TIBC of 230 µg/ml would result in an iron value of appoximately 48 µg/dL.)

Statistically significant reductions in the percent transferrin saturation and ferritin, occurred after 6 and 8 months, respectively. Significant increases in erythropoietin dose requirements was also seen after 8 months.

Marked increases in serum transferrin receptor concentrations, which correlated with developing iron deficiency and increasing erythropoietin dose, were also reported (data not shown).

Oral iron absorption studies were performed in a subset of 20 dialysis patients in this study. In these studies, 60 mg of elemental iron was given with 100 mg of Vitamin C to fasting subjects, and iron absorption was calculated from changes in serum iron concentrations. Six of these patients had a transferrin saturation of <10%, and five out of these six patients demonstrated "adequate" iron absorption, as defined as absorbing more than 3.5 mg of iron.

Safety data were not collected for patients in the historical control population. Control safety data was taken from a review chapter by Levin NW et. al., "Complications During Hemodialysis" in Clinical Dialysis (2nd edition, Norwalk, Appleton and Lange, 1990). This review article categorized the adverse events associated with hemodialysis with respect to patient age, sex, diabetic status, and dialyzer reuse status (vol. 25, pp. 267-296). As per the sponsor (vol. 16, p. 86): *Representative percentages from the data of Levin et. al. were thus selected for calculation of adverse events in the historical control group. For each adverse event, the reported frequency was multiplied by 25 (the number of patients in the historical control study) and the result rounded to the nearest whole. This number was then reported as the incidence of the adverse event, and the frequency for that adverse event was recalculated based on its incidence.*

Investigators and Study Centers

Investigators and study centers for study 5600-01 were:

Allen Nissenson, MD
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Dr. Seligman was also the principal investigator for the historical control study.

[redacted]

STUDY RESULTS

Patient Disposition

The intent-to-treat population consisted of 39 patients in the low-dose Ferrlecit group, 44 patients in the high-dose Ferrlecit group, and 25 historical control patients.

A total of 5 patients were withdrawn from the study. Two discontinued for logistic reasons: one discontinued following the test dose, and one patient in the low-dose group discontinued following the sixth dose of study drug. One patient was withdrawn after development of pruritis and chest pain following the test dose. One patient in the high-dose group was withdrawn following the development of nausea, abdominal pain, flank pain, fatigue, and rash following the first treatment dose. One patient in the low-dose group was withdrawn after the development of a "red, blotchy rash" following the first dose.

Although the protocol recommended that investigators maintain the same EPO dose throughout the study, the EPO dose was changed 24 times for 22 of the 83 intent-to-treat patients. Two patients required 2 dosage adjustments each.

Ten EPO dosage changes were required during the course of study drug administration (i.e. prior to or on Day 19). Specifically, there were 4 patients who had increases, and 2 patients who had decreases in their EPO doses in the low-dose group; and 3 patients who had increases, and 1 patient who had a decrease in their EPO doses in the high-dose group.

Fourteen EPO dosage changes occurred after the administration of study drug (i.e. between Day 19 and Day 47). Specifically, 6 patients had increases, and 2 patients had reductions in the low-dose group; and 2 patients had increases, and 4 patients had reductions in the high-dose group.

A list of patients who received EPO dosage changes before Day 19, and between Days 19 and 47, are shown below (vol. 10.1, p. 4). Note that the specific dates of these dosage changes were not recorded.

EPO Dosage Changes Before Day 19, and Between Days 19 and 47

Patient Number	Dose Increase (+) or Decrease (-)	
	Day 19	Day 19 to Day 47
007	(+) 1500	
101		(+) 2000
106		(-) 10000
109		(+) 6000
113	(+) 2000	
115	(+) 2000	
118	(-) 6000	(+) 6000
123	(+) 10000	
132		(-) 2000
136		(+) 2000
141	(+) 2000	
144		(-) 4000
305	(+) 1000	
306		(+) 2000
308		(-) 1000
310		(+) 1000
313	(+) 1000	
315	(-) 1000	
326	(-) 4000	
330		(+) 5000
332		(+) 2000
338		(-) 1000

Three patients in the low-dose group were enrolled but did not meet the inclusion criteria (hemoglobin or ferritin levels were too high).

Thus, the per-protocol population consisted of 24 low-dose Ferrlecit patients, 35 high-dose Ferrlecit patients, and 25 historical control patients. These numbers represent 59%, 78%, and 100%, of the intent-to-treat low-dose, high-dose, and historical control populations, respectively.

Patient Demographics and Other Baseline Variables

Intent-to-Treat Population

Patients were of mean age 55 years, height 65 inches (height data was not available for historical control patients), weight 158 lbs, and 59% were female. Approximately 19% of female patients were > 65 years of age, as were 11% of male patients. The above demographics were similar across treatment and historical control groups.

There were more white patients in the low- and high-dose Ferrlecit groups, compared to historical control patients (75% of Ferrlecit patients, compared to 40% of historical control patients).

Mean systolic blood pressure was higher in historical control patients (average of 150 mm Hg in Ferrlecit patients, compared to 170 mm Hg in historical control patients).

The mean baseline hemoglobin and hematocrit were similar between treatment and historical control patients, and were 9.6 g/dL, and 29%, respectively.

Baseline values for percent iron saturation, serum ferritin, serum iron, and red blood cell indices varied between treatment groups and when compared to the historical control. These values are summarized below (vol. 16, p. 28).

Baseline Iron Studies and Red Blood Cell Indices

Variable	Treatment Group: 500 mg (N = 41)	1000 mg (N = 47)	Control (N = 25)	p-value*: 500 vs. 1000	500 vs. Control	1000 vs. Control	Overall
Baseline Percent Iron Saturation (%)							
n	38	43	25	0.026	0.012	0.630	0.010
Mean (Std)	20.1 (11.9)	15.6 (7.5)	14.2 (4.4)				
Min	4.0	2.0	6.7				
Max	58.0	35.0	27.3				
Baseline Serum Ferritin (ng/mL)							
n	37	43	32	0.670	<0.001	<0.001	<0.001
Mean (Std)	185.6 (116.3)	88.4 (143.2)	605.6 (390.9)				
Min	39.0	8.0	61.0				
Max	660.0	941.0	1000				
Baseline Serum Iron (ug/dL)							
n	39	44	25	0.112	0.007	0.162	0.024
Mean (Std)	49.7 (29.7)	41.6 (22.4)	33.5 (13.6)				
Min	11.0	6.0	16.0				
Max	112.0	101.0	81.0				
Baseline MCH (pg)							
n	40	44	25	0.691	0.055	0.022	0.060
Mean (Std)	30.0 (3.2)	29.7 (2.2)	31.4 (3.3)				
Min	20.0	25.0	26.6				
Max	35.0	34.0	39.1				
Baseline MCV (fl)							
n	40	43	25	0.705	0.001	<0.001	<0.001
Mean (Std)	89.5 (7.7)	88.9 (5.3)	96.0 (9.0)				
Min	67.0	72.6	84.6				
Max	103.6	100.1	116.7				
Baseline MCHC (g/dL)							
n	40	44	25	0.566	0.036	0.009	0.028
Mean (Std)	33.4 (1.3)	33.5 (1.2)	32.7 (0.6)				
Min	30.0	31.0	31.4				
Max	35.3	36.0	34.2				

* For a continuous variable, an ANOVA model with effects for treatment group was used to compare the group means, and the p-value was associated with the F test. For a categorical variable, the p-value was associated with the Fisher's Exact Test.

Overall, patient populations were similar with respect to baseline demographics, hemoglobin, hematocrit, iron studies, and red blood cell indices. Of note, the baseline serum ferritin was higher in the historical control (606 ng/mL), compared to Ferrlecit-treated patients (88 ng/mL in the high-dose group, and 106 ng/mL in the low-dose group).

Efficacy Analysis

Intent-to-Treat Population

Mean Change in Hemoglobin

The primary efficacy variable was the change in hemoglobin from baseline to endpoint (last available observation through Day 40). These data were analyzed by an ANOVA model, which included the factors of dose group, study center, and the interaction of dose group and study center. If the interaction was not significant, the analysis was rerun, and a model that did not include the interaction term was used. The significance of the

mean change from baseline to endpoint for each dose group was determined using a paired t-test.

The results of the ANOVA analysis for mean change in hemoglobin is shown below (Table 4, vol. 16, p. 101).

Mean Change in Hemoglobin
ANOVA Analysis

	Treatment Group		
Change in Hemoglobin	500 mg (N = 39)	1000 mg (N = 44)	p-value*
n	39	44	0.001
Mean	0.3	1.1	
Std	1.1	1.1	
Min	-2.4	-1.1	
Max	3.0	3.6	
c.i.	(0.0, 0.6)	(0.8, 1.4)	
Probt+	0.072	<0.001	

Note: The tmt*inv interaction from a preliminary model was not significant (p=0.136).
* p-value is associated with an F test by using the ANOVA with effects of center and treatment.
\+ p-value is associated with the paired t-test.

The mean changes in hemoglobin from baseline to last available observation through Day 40, was greater for the high-dose (1.1 g/dL), compared to the low-dose (0.3 g/dL) groups, (p=0.001, ANCOVA). The mean changes in hemoglobin from baseline also increased in both dose groups (p=0.072 for low-dose patients, and p<0.001 for high-dose patients; paired t-test). The overall treatment-by-investigator interaction was not statistically significant (p=0.136).

A secondary analysis of the primary efficacy variable (of the change in hemoglobin from baseline), was a Repeated Measures ANOVA analysis. This analysis examined the change in mean hemoglobin from baseline to each of the regularly scheduled laboratory assessments. A last-observation-carried-forward approach was used to replace any missing data. The model included the factors of dose group, subject within the dose group, visit, and the interaction of dose group and visit. A summary of the results of this analysis is shown below (Table 5, vol. 16, p. 32).

Mean Change in Hemoglobin
Repeated Measures Analysis

Variable	500-mg Treatment			1000-mg Treatment			p-values*		
	Day 19	Day 31	Day 47	Day 19	Day 31	Day 47	TMT	DAY	TMT*DAY
Hemoglobin (g/dL)									
N	39	39	39	44	44	44	0.002	0.020	0.749
Mean	0.3	0.3	0.5	1.0	1.1	1.3			
Std	1.2	1.1	1.2	0.9	1.1	1.2			
Min	-1.9	-2.4	-1.9	-0.8	-1.1	-1.6			
Max	3.2	3.0	3.8	2.6	3.6	3.7			

* p-values are from a mixed model with fixed effects for treatment, day, and treatment*day interaction and a random effect of patient nested within treatment.

The mean change in hemoglobin was consistently higher in the high-dose group, (p=0.002, mixed model; fixed treatment effect).

No significant interactions of age, race, or gender, with the change in hemoglobin, were observed (vol. 16, p. 106).

Mean Changes in Hematocrit, Iron Studies, and Red Blood Cell Indices

The results of the ANOVA analysis of changes in hematocrit, iron studies, and red blood cell indices, from baseline to the last available observation through Day 40, are shown below (Table 6, vol. 16, p. 105).

**Mean Changes in Hematocrit, Iron Studies, and RBC Indices
Results of ANOVA Analysis**

Variable	Treatment Group 500 mg (N = 39)	1000 mg (N = 44)	p-value*
Hematocrit (%)			
n	39	44	0.002
Mean	1.4	3.6	
Std	3.4	3.1	
Min	-8.0	-3.0	
Max	10.0	10.0	
c.i.	(0.4, 2.3)	(2.6, 4.4)	
Probt+	0.018	<0.001	
Percent Iron Saturation (%)			
n	38	43	0.017
Mean	2.8	8.5	
Std	11.9	10.5	
Min	-29.0	-15.0	
Max	27.0	45.0	
c.i.	(-0.5, 6.0)	(5.8, 11.2)	
Probt+	0.156	<0.001	
Serum Ferritin (ng/mL)			
n	37	43	0.153
Mean	132.0	199.4	
Std	248.4	186.9	
Min	-11.0	0.0	
Max	1282	938.0	
c.i.	(63.1,201.0)	(159.1,239.6)	
Probt+	0.003	<0.001	
Serum Iron (ug/dL)			
n	39	44	0.141
Mean	3.7	11.7	
Std	28.0	24.6	
Min	-78.0	-45.0	
Max	69.0	77.0	
c.i.	(-3.9, 11.2)	(5.5, 17.9)	
Probt+	0.418	0.003	
MCH (pg)			
n	39	44	0.023
Mean	-0.1	0.6	
Std	1.3	1.3	
Min	-3.7	-2.0	
Max	2.0	5.0	
c.i.	(-0.4, 0.3)	(0.2, 0.9)	
Probt+	0.712	0.007	
MCV (fl)			
n	39	43	0.013
Mean	0.7	2.3	
Std	2.6	2.9	
Min	-5.0	-4.1	
Max	6.3	12.6	
c.i.	(-0.0, 1.4)	(1.5, 3.0)	
Probt+	0.102	<0.001	
MCHC (g/dL)			
n	39	44	0.372
Mean	-0.5	-0.2	
Std	2.1	1.0	
Min	-11.0	-2.5	
Max	2.0	2.0	
c.i.	(-1.1, 0.1)	(-0.4, 0.1)	
Probt+	0.150	0.225	

* p-value is associated with the ANOVA.
\+ p-value is associated with the paired t-test.

The mean changes from baseline for the following parameters were small, and higher for the high-dose, compared to low-dose groups for the: hematocrit (3.6% in the high-dose, compared to 1.4% in the low-dose group; p=0.002, ANOVA), and percent iron

saturation (8.5% in the high-dose group, compared to 2.8% in the low-dose group; p=0.017, ANOVA).

For the low-dose group, a small within-group increase in the hematocrit (1.4%; p=0.018, paired t-test), and a within-group increase in serum ferritin (132 ng/mL; p=0.003, paired t-test), were seen.

For the high-dose group, small within-group increases in the hematocrit (3.6%; p<0.001, paired t-test), serum iron (11.7 µg/dL; p=0.003, paired t-test), percent iron saturation (8.5%; p<0.001, paired t-test), were seen. An increase in the serum ferritin (199.4 ng/mL; p<0.001, paired t-test), was also observed.

The results of a Repeated Measures ANOVA analysis of changes in hematocrit, iron studies, and red blood cell indices, from baseline to each of the regularly schedule laboratory assessments, are shown below (Table 5, vol. 16, pp. 102-3).

Mean Changes in Hematocrit, Iron Studies, and RBC Indices
Repeated Measures Analysis

	500-mg Treatment			1000-mg Treatment			p-values*		
Variable	Day 19	Day 31	Day 47	Day 19	Day 31	Day 47	TMT	DAY	TMT*DAY
Hematocrit (%)									
n	39	39	39	44	44	44	0.003	0.231	0.043
Mean	1.1	1.4	1.4	3.1	3.6	3.5			
Std	3.6	3.4	3.8	3.6	3.1	3.7			
Min	-5.0	-8.0	-7.0	-2.0	-3.0	-5.0			
Max	11.0	10.0	12.0	9.0	10.0	12.0			
Percent Iron Saturation (%)									
n	36	38	38	43	43	43	0.001	0.008	0.479
Mean	1.2	2.8	-0.6	9.0	8.5	5.5			
Std	9.6	11.9	10.2	8.6	10.5	11.3			
Min	-26.0	-29.0	-25.0	-11.0	-15.0	-21.0			
Max	19.0	27.0	26.0	28.0	45.0	32.0			
Serum Ferritin (ng/mL)									
n	36	37	37	43	43	43	0.001	<0.001	0.002
Mean	130.3	132.0	65.0	319.7	199.4	133.7			
Std	68.0	248.4	144.2	212.7	156.9	180.6			
Min	23.0	-11.0	-179	92.0	8.0	-39.0			
Max	288.0	1282	718.0	1170	938.0	962.0			
Serum Iron (ug/dL)									
n	38	39	39	44	44	44	0.029	0.015	0.162
Mean	-1.2	3.7	-3.1	13.9	11.7	6.3			
Std	25.0	30.0	27.0	28.7	34.6	26.1			
Min	-76.0	-76.0	-74.0	-28.0	-45.0	-67.0			
Max	51.0	69.0	43.0	61.0	77.0	75.0			
MCH (pg)									
n	38	39	39	40	44	44	0.058	0.415	0.567
Mean	0.1	-0.1	0.2	1.9	0.6	0.9			
Std	0.8	1.3	1.2	9.1	1.3	1.4			
Min	-2.0	-3.7	-2.0	-1.1	-2.0	-2.0			
Max	2.0	2.0	3.0	58.0	5.0	5.0			
MCV (fl)									
n	38	39	39	39	43	43	0.002	0.182	0.003
Mean	0.8	0.7	-0.1	1.7	2.3	2.5			
Std	2.0	2.6	3.3	3.3	2.9	3.5			
Min	-3.0	-5.0	-9.2	-3.7	-4.1	-4.1			
Max	7.1	6.3	6.3	8.3	12.6	13.6			
MCHC (g/dL)									
n	38	39	39	40	44	44	0.642	0.003	0.240
Mean	-0.0	-0.5	0.1	-0.2	-0.2	0.3			
Std	0.9	2.1	2.0	0.7	1.0	0.8			
Min	-2.0	-11.0	-11.0	-2.0	-3.5	-1.1			
Max	2.0	2.0	2.0	1.0	3.0	2.0			

* p-values are from a mixed model with fixed effects for treatment, day, and treatment*day interaction and a random effect of patient nested within treatment.

Mean changes from baseline for hematocrit, serum iron, percent iron saturation, and serum ferritin were higher in the high-dose, compared to the low-dose treatment group (p= 0.003, 0.029, 0.001, and 0.001, respectively; mixed model/fixed treatment effect). Notably, maximum increases in hematocrit were seen by Day 31, while maximum increases in iron study values were seen by Day 19.

Significant interactions between treatment group and visit day were seen for serum ferritin and MCV (p=0.002, and 0.003, respectively; mixed model/fixed effect for treatment*day interaction).

Per-Protocol Population

The results of the ANOVA analysis of mean change in hemoglobin, from baseline to the last observation through Day 40, for those patients who completed the study per protocol, is shown below (Table 7, vol. 16, p. 106).

Mean Change in Hemoglobin for Per-Protocol Patients
ANOVA Analysis

Variable	Treatment Group: 500 mg (N = 24)	1000 mg (N = 15)	p-value*
Hemoglobin (g/dL)			
n	24	35	0.013
Mean	0.5	1.2	
Std	1.0	1.1	
Min	-2.4	-1.1	
Max	2.0	3.6	
c.i.	(0.1, 0.8)	(0.9, 1.5)	
Probt+	0.024	<0.001	

* p-value is associated with the ANOVA.
\+ p-value is associated with the paired t-test.

The mean increase in hemoglobin from baseline was greater for the high-dose (1.2 g/dL), compared to the low-dose (0.5 g/dL) group (p=0.013, ANOVA).

The mean changes in hemoglobin from baseline increased within both dose groups (p=0.024 for the low-dose group, paired t-test, and p<0.001 for the high-dose group, paired t-test).

The results of the Repeated Measures ANOVA analysis of mean change in hemoglobin, from baseline to each of the regularly scheduled laboratory assessments, is shown below (Table 8, vol. 16, p. 108).

**Mean Change in Hemoglobin for Per-Protocol Patients
Repeated Measures Analysis**

Variable	500-mg Treatment			1000-mg Treatment			p-values*		
	Day 19	Day 31	Day 47	Day 19	Day 31	Day 47	TMT	DAY	TMT*DAY
Hemoglobin (g/dL)									
n	24	24	24	35	35	35	0.018	0.158	0.311
Mean	0.5	0.5	0.6	1.0	1.2	1.3			
Std	1.1	1.0	1.2	0.9	1.1	1.2			
Min	-1.3	-2.4	-1.9	-0.8	-1.1	-1.6			
Max	3.2	2.0	2.6	2.6	3.6	3.7			

* p-values are from a mixed model with fixed effects for baseline, treatment, day, and treatment*day interaction and a random effect of patient nested within treatment.

The mean change in hemoglobin was higher in the high-dose group (p=0.018, mixed model;fixed treatment effect).

The results of the ANOVA analysis of changes in hematocrit, iron studies, and red blood cell indices, from baseline to the last available observation through Day 40, are shown below (Table 9, vol. 16, p. 110).

**Mean Changes in Hematocrit, Iron Studies, and RBC Indices
Results of ANOVA Analysis**

Variable	Treatment Group 500 mg (N = 24)	1000 mg (N = 35)	p-value*
Hematocrit (%)			
n	24	35	0.028
Mean	1.9	3.7	
Std	3.3	3.3	
Min	-8.0	-3.0	
Max	7.0	10.0	
c.i.	(0.7, 3.0)	(2.8, 4.7)	
Probt+	0.011	<0.001	
Percent Iron Saturation (%)			
n	24	34	0.076
Mean	4.1	8.3	
Std	11.6	10.5	
Min	-29.0	-15.0	
Max	27.0	45.0	
c.i.	(0.1, 8.2)	(5.2, 11.4)	
Probt+	0.095	<0.001	
Serum Ferritin (ng/mL)			
n	23	34	0.012
Mean	87.6	175.1	
Std	138.3	105.6	
Min	-11.0	0.0	
Max	691.0	391.0	
c.i.	(28.1,137.1)	(144.5,205.7)	
Probt+	0.006	<0.001	
Serum Iron (ug/dL)			
n	24	35	0.368
Mean	6.6	10.8	
Std	27.1	24.3	
Min	-57.0	-45.0	
Max	69.0	77.0	
c.i.	(-2.9, 16.1)	(3.8, 17.8)	
Probt+	0.266	0.013	
MCH (pg)			
n	24	35	0.092
Mean	0.1	0.7	
Std	1.4	1.4	
Min	-3.7	-2.0	
Max	2.0	5.0	
c.i.	(-0.4, 0.5)	(0.3, 1.1)	
Probt+	0.851	0.008	
MCV (fl)			
n	24	34	0.039
Mean	0.7	2.3	
Std	2.8	3.1	
Min	-5.0	-6.1	
Max	5.6	12.6	
c.i.	(-0.3, 1.7)	(1.4, 3.2)	
Probt+	0.235	<0.001	
MCHC (g/dL)			
n	24	35	0.662
Mean	-0.2	-0.1	
Std	1.3	1.8	
Min	-5.1	-2.5	
Max	2.0	2.0	
c.i.	(-0.6, 0.2)	(-0.4, 0.2)	
Probt+	0.441	0.614	

* p-value is associated with the ANOVA.
\+ p-value is associated with the paired t-test.

The mean change in hematocrit from baseline was small, and higher for the high-dose (3.7%), compared to the low-dose group (1.9%; p=0.028, ANOVA). The increase in serum ferritin was also higher for the high-dose (175.1 ng/ml), compared to the low-dose group (87.6 ng/ml; p=0.012, ANOVA).

For the low-dose group, a small within-group increase in the hematocrit (1.9%; p=0.011, paired t-test), and a within-group increase in the serum ferritin (87.6 ng/ml; p=0.006, paired t-test), were observed.

For the high-dose group, small within-group increases in the hematocrit (3.7%; p<0.001, paired t-test), serum iron (10.8 µg/dL; p=0.013, paired t-test), and percent iron saturation (8.3%; p<0.001, paired t-test), were observed. The serum ferritin also increased by 175.1 ng/ml (p<0.001, paired t-test).

The results of a Repeated Measures ANOVA analysis of changes in hematocrit, iron studies, and red blood cell indices, from baseline to each of the regularly scheduled laboratory assessments, are shown below (Table 8, vol. 16, pp. 108-9).

Mean Changes in Hematocrit, Iron Studies, and RBC Indices
Repeated Measures Analysis

Variable	500-mg Treatment			1000-mg Treatment			p-values*		
	Day 19	Day 31	Day 47	Day 19	Day 31	Day 47	TMT	DAY	TMT*DAY
Hematocrit (%)									
n	24	24	24	35	35	35	0.030	0.210	0.650
Mean	1.5	1.9	1.6	3.0	3.7	3.7			
Std	3.3	3.3	3.8	2.6	3.3	3.6			
Min	-3.0	-8.0	-7.0	-2.0	-3.0	-5.0			
Max	11.0	7.0	8.0	9.0	10.0	12.0			
Percent Iron Saturation (%)									
n	24	24	24	34	34	34	0.030	0.015	0.313
Mean	1.8	4.1	0.9	8.9	8.3	4.6			
Std	9.4	11.6	8.6	9.0	10.5	10.2			
Min	-18.0	-29.0	-25.0	-11.0	-15.0	-21.0			
Max	19.0	27.0	13.0	28.0	45.0	32.0			
Serum Ferritin (ng/mL)									
n	23	23	23	34	34	34	<0.001	<0.001	0.001
Mean	119.3	87.6	44.3	310.3	175.1	135.4			
Std	62.6	138.3	93.8	215.9	105.6	99.8			
Min	24.0	-11.0	-42.0	92.0	0.0	-39.0			
Max	258.0	691.0	385.0	1170	391.0	362.0			
Serum Iron (ug/dL)									
n	24	24	24	35	35	35	0.222	0.110	0.072
Mean	0.2	6.6	2.0	13.8	10.8	5.1			
Std	33.8	27.1	22.3	21.2	24.3	25.1			
Min	-72.0	-87.0	-52.0	-28.0	-45.0	-67.0			
Max	53.0	69.0	43.0	61.0	77.0	75.0			
MCH (pg)									
n	23	24	24	31	35	35	0.042	0.249	0.776
Mean	0.1	0.1	0.2	0.5	0.7	0.9			
Std	1.0	1.4	1.1	0.8	1.4	1.4			
Min	-2.0	-3.7	-2.0	-1.0	-2.0	-2.0			
Max	2.0	2.0	2.0	2.7	5.0	5.0			
MCV (fl)									
n	23	24	24	30	34	34	0.017	0.254	0.030
Mean	0.9	0.7	-0.2	1.8	2.3	2.4			
Std	3.2	2.8	3.0	2.4	3.1	3.6			
Min	-3.0	-5.0	-7.0	-3.7	-4.1	-4.1			
Max	7.1	5.6	5.1	8.3	12.6	13.6			
MCHC (g/dL)									
n	23	24	24	31	35	35	0.800	0.002	0.525
Mean	0.0	-0.2	0.4	-0.2	-0.1	0.3			
Std	0.9	1.3	0.9	0.7	1.0	0.7			
Min	-2.0	-5.1	-1.0	-2.0	-2.5	-1.0			
Max	2.0	2.0	2.0	1.0	2.0	2.0			

* p-values are from a mixed model with fixed effects for baseline, treatment, day, and treatment*day interaction and a random effect of patient nested within treatment.

Mean changes from baseline for hematocrit, percent iron saturation, and serum ferritin were higher in the high-dose, compared to the low-dose treatment group (p=0.030, 0.030, <0.001, 0.017, and 0.042, respectively; mixed model/fixed treatment effect). Notably, maximum increases in the hematocrit were seen by Day 31, while maximum increases in iron study values were seen by Day 19.

A significant interation between treatment group and visit day was seen for the serum ferritin(p=0.001; mixed model/fixed effect for treatment*day interaction).

Comparison to Historical Control

Intent-to-Treat Population

Mean Change in Hemoglobin

The change in hemoglobin from baseline to endpoint (last available observation through Day 40). These data were analyzed by using an ANCOVA. This model included the factors of treatment group (low-dose, high-dose, and control), baseline hemoglobin, and the interaction of treatment and baseline hemoglobin. If the interaction was not significant, the analysis was rerun using a model that did not include the interaction term.

The results of the ANCOVA analysis of mean change in hemoglobin is shown below (Table 10, vol. 16, p. 117).

Mean Change in Hemoglobin
ANCOVA Analysis

	Treatment Group			p-values*		
Variable	500 mg (N = 39)	1000 mg (N = 44)	Control (N = 25)	500 vs. 1000	500 vs. Control	1000 vs. Control
Hemoglobin (g/dL)						
n	39	44	24			
Mean	0.3	1.1	0.4	0.002	0.501	0.001
Std	1.1	1.1	0.9			
Min	-2.4	-1.1	-1.1			
Max	3.0	3.6	2.8			
c.i.	(0.0, 0.6)	(0.8, 1.4)	(0.2, 0.7)			
Probt+	0.072	<0.001	0.016			

* p-value is associated with the ANCOVA.
\+ p-value is associated with the paired t-test.

The mean change in hemoglobin from baseline to last available observation through Day 40, was greater in the high-dose group (1.1 g/dL), compared to the low-dose group (0.3 g/dL;

p=0.002, ANCOVA), and compared to the historical control group (0.4 g/dL; p=0.001, ANCOVA). No difference in mean change in hemoglobin was observed between the low-dose and historical control groups.

Small increases in hemoglobin from baseline to last available observation through Day 40, were seen for the high-dose group (p<0.001, paired t-test), and for the historical control group (p=0.016, paired t-test).

Results from the individual investigator sites are shown below (Table 10a, vol. 16, p. 117).

Mean Change in Hemoglobin by Treatment Site
ANCOVA Analysis

Variable	Treatment Group 500 mg (N = 39)	1000 mg (N = 44)	Control (N = 25)	p-values* 500 vs. 1000	500 vs. Control	1000 vs. Control
Lindsay						
n	17	19	24	<0.001	0.167	0.013
Mean	-0.3	0.9	0.4			
Std	1.0	1.1	0.9			
Min	-2.4	-1.0	-1.1			
Max	1.6	2.8	2.8			
c.i.	(-0.7, 0.1)	(0.5, 1.3)	(0.2, 0.7)			
Probt+	0.159	0.002	0.016			
Nissenson						
n	17	20	24	0.166	0.104	0.002
Mean	0.7	1.3	0.4			
Std	0.9	1.2	0.9			
Min	-0.6	-1.1	-1.1			
Max	3.0	3.6	2.8			
c.i.	(0.3, 1.1)	(0.8, 1.8)	(0.2, 0.7)			
Probt+	0.005	0.000	0.016			
Swan						
n	5	5	24	0.983	0.084	0.081
Mean	1.2	1.1	0.4			
Std	0.9	0.6	0.9			
Min	-0.3	0.4	-1.1			
Max	2.0	1.7	2.8			
c.i.	(0.3, 2.0)	(0.5, 1.6)	(0.2, 0.7)			
Probt+	0.041	0.014	0.016			

* p-value is associated with the ANCOVA.
\+ p-value is associated with the paired t-test.

Significant differences between the high- and low-dose groups (p<0.001, ANCOVA), and between the high-dose and historical control control groups (p=0.013, ANCOVA), occurred at the Lindsay site. At the Nissenson site, a significant difference occurred between the high-dose and historical control groups (p=0.002, ANCOVA). Differences between the low-dose and historical control groups were not significant at any site.

Mean Changes in Hematocrit, Iron Studies, and Red Blood Cell Indices

The results of the ANCOVA analysis of changes in hematocrit, iron studies, and red blood cell indices, from baseline to the last available observation through Day 40, are shown below (Table 11, vol. 16, pp. 118-19).

Mean Changes in Hematocrit, Iron Studies, and RBC Indices
ANCOVA Analysis

Variable	Treatment Group: 500 mg (N = 39)	1000 mg (N = 44)	Control (N = 25)	p-values*: 500 vs. 1000	500 vs. Control	1000 vs. Control
Hematocrit (%)						
n	38	44	24	0.002	0.140	<0.001
Mean	1.4	3.6	0.8			
Std	3.4	3.1	2.4			
Min	-8.0	-3.0	-3.0			
Max	10.0	10.0	7.3			
c.i.	(0.4, 2.3)	(2.8, 4.4)	(-0.0, 1.6)			
Probt+	0.018	<0.001	0.112			
Percent Iron Saturation (%)						
n	38	43	24	0.193	0.967	0.227
Mean	2.8	8.5	6.1			
Std	11.9	10.5	12.4			
Min	-29.0	-15.0	-3.6			
Max	27.0	45.0	55.8			
c.i.	(-0.5, 6.0)	(5.8, 11.2)	(1.8, 10.5)			
Probt+	0.156	<0.001	0.024			
Serum Ferritin (ng/mL)						
n	37	43	.§	0.134	NA§	NA
Mean	132.0	199.4				
Std	248.4	156.9				
Min	-11.0	0.0				
Max	1282	938.0				
c.i.	(63.1,201.0)	(159.1,239.6)				
Probt+	0.003	<0.001				
Serum Iron (ug/dL)						
n	39	44	25	0.553	0.651	0.962
Mean	3.7	11.7	16.2			
Std	28.0	24.6	31.5			
Min	-78.0	-45.0	-8.0			
Max	69.0	77.0	151.0			
c.i.	(-3.9, 11.2)	(5.5, 17.9)	(5.5, 27.0)			
Probt+	0.418	0.003	0.016			
MCH (pg)						
n	39	44	24	0.040	0.985	0.084
Mean	-0.1	0.6	-0.3			
Std	1.3	1.3	1.6			
Min	-3.7	-2.0	-6.0			
Max	2.0	5.0	2.1			
c.i.	(-0.4, 0.3)	(0.2, 0.9)	(-0.9, 0.3)			
Probt+	0.712	0.007	0.385			
MCV (fl)						
n	39	43	24	0.042	0.004	<0.001
Mean	0.7	2.3	-2.6			
Std	2.6	2.9	4.7			
Min	-5.0	-4.1	-21.3			
Max	6.3	12.6	1.8			
c.i.	(-0.0, 1.4)	(1.5, 3.0)	(-4.2, -1.0)			
Probt+	0.102	<0.001	0.011			
MCHC (g/dL)						
n	39	44	24	0.222	0.019	0.169
Mean	-0.5	-0.2	0.6			
Std	2.1	1.0	0.5			
Min	-11.0	-2.5	-0.5			
Max	2.0	2.0	1.5			
c.i.	(-1.1, 0.1)	(-0.6, 0.1)	(0.4, 0.8)			
Probt+	0.150	0.225	<0.001			

* p-value is associated with the ANCOVA.
\+ p-value is associated with the paired t-test.
§ - = No data available.
§ NA = Not Applicable.

The mean increase in hematocrit was greater in the high-dose group (3.6%), compared to the low-dose group (1.4%; p=0.002, ANCOVA), and greater than that seen in the historical control (0.8%; p<0.001, ANCOVA). Changes in iron studies from baseline were not significantly different between treatment groups.

In the high-dose group, within-group increases from baseline were observed for the hematocrit (3.6%; p<0.001, paired t-test), serum iron (11.7 µg/dL; p=0.003, paired t-test), percent iron saturation (8.5%; p<0.001, paired t-test), and serum ferritin (199.4 ng/ml; p<0.001, paired t-test).

In the low-dose group, within-group increases from baseline were observed for the hematocrit (1.4%; p=0.018, paired t-test), and serum ferritin (132 ng/ml; p=0.003, paired t-test).

In the historical control, small within-group increases from baseline were seen for the serum iron (16.2 µg/dL; p=0.016, paired t-test), and percent iron saturation (6.1%; p=0.024, paired t-test).

Comparison to Historical Control

Per-Protocol Population [BEST POSSIBLE]

The results of the ANCOVA analysis of mean change in hemoglobin from baseline to the last available observation through Day 40 is shown below (Table 12, vol. 16, p. 51).

Mean Change in Hemoglobin
ANCOVA Analysis

Variable	Treatment Group			p-values*		
	500 mg (N = 24)	1000 mg (N = 35)	Control (N = 25)	500 vs. 1000	500 vs. Control	1000 vs. Control
Hemoglobin (g/dL)						
n	24	35	24			
Mean	0.5	1.2	0.4	0.009	0.337	<0.001
Std	1.0	1.1	0.9			
Min	-2.4	-1.1	-1.1			
Max	2.0	3.6	2.8			
c.i.	(0.1, 0.8)	(0.9, 1.5)	(0.2, 0.7)			
Probt+	0.024	<0.001	0.016			

* p-value is associated with the ANCOVA.
\+ p-value is associated with the paired t-test.

The mean change in hemoglobin from baseline to last available observation through Day 40, was greater in the high-dose group (1.2 g/dL), compared to the low-dose group (0.5 g/dL;

p=0.009, ANCOVA), and higher than that seen in the historical control group (0.4 g/dL; p<0.001, ANCOVA). No difference in the mean change in hemoglobin was observed between the low-dose and historical control groups.

Small within-group increases in hemoglobin from baseline to last available observation through Day 40, were seen for all three groups (p=0.024, <0.001, and 0.016 for the low-dose, high-dose, and historical control groups, respectively; paired t-test).

The results of the ANCOVA analysis of changes in hematocrit, iron studies, and red blood cell indices, from baseline to the last available observation through Day 40, are shown below (Table 13, vol. 16, pp. 123-24).

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Mean Changes in Hematocrit, Iron Studies, and RBC Indices
ANCOVA Analysis

Variable	Treatment Group: 500 mg (N = 24)	1000 mg (N = 35)	Control (N = 25)	p-values*: 500 vs. 1000	500 vs. Control	1000 vs. Control
Hematocrit (%)						
n	24	35	24	0.026	0.065	<0.001
Mean	1.9	3.7	0.8			
Std	3.3	3.3	2.4			
Min	-8.0	-3.0	-3.0			
Max	7.0	10.0	7.3			
c.i.	(0.7, 3.0)	(2.8, 4.7)	(-0.0, 1.6)			
Probt+	0.011	<0.001	0.112			
Percent Iron Saturation (%)						
n	24	34	24	0.333	0.894	0.264
Mean	4.1	8.1	6.1			
Std	11.6	10.5	12.4			
Min	-29.0	-15.0	-3.6			
Max	27.0	45.0	55.8			
c.i.	(0.1, 8.2)	(5.2, 11.4)	(1.8, 10.5)			
Probt+	0.095	<0.001	0.024			
Serum Ferritin (ng/mL)						
n	23	34	-[$]	0.007	NA[$]	NA
Mean	87.6	175.1				
Std	138.3	105.6				
Min	-11.0	0.0				
Max	691.0	391.0				
c.i.	(38.1,137.1)	(144.5,205.7)				
Probt+	0.006	<0.001				
Serum Iron (ug/dL)						
n	24	35	25	0.676	0.689	0.981
Mean	6.6	10.8	16.2			
Std	27.1	24.3	31.5			
Min	-57.0	-65.0	-8.0			
Max	69.0	77.0	151.0			
c.i.	(-2.9, 16.1)	(3.8, 17.8)	(5.5, 27.0)			
Probt+	0.246	0.013	0.016			
MCH (pg)						
n	24	35	24	0.063	0.990	0.068
Mean	0.1	0.7	-0.1			
Std	1.4	1.4	1.6			
Min	-3.7	-2.0	-6.0			
Max	2.0	5.0	2.1			
c.i.	(-0.4, 0.5)	(0.3, 1.1)	(-0.9, 0.3)			
Probt+	0.851	0.008	0.385			
MCV (fl)						
n	24	34	24	0.056	0.054	<0.001
Mean	0.7	2.3	-2.6			
Std	2.8	3.1	4.7			
Min	-6.0	-4.1	-21.3			
Max	5.6	12.6	1.8			
c.i.	(-0.3, 1.7)	(1.4, 3.2)	(-4.2, -1.0)			
Probt+	0.235	<0.001	0.011			
MCHC (g/dL)						
n	24	35	24	0.480	0.013	0.064
Mean	-0.2	-0.1	0.6			
Std	1.1	1.0	0.5			
Min	-5.1	-2.5	-0.5			
Max	2.0	2.0	1.5			
c.i.	(-0.6, 0.2)	(-0.4, 0.2)	(0.4, 0.8)			
Probt+	0.441	0.514	<0.001			

* p-value is associated with the ANCOVA.
\+ p-value is associated with the paired t-test.
[$] - = No data available.
[$] NA = Not Applicable.

The mean change from baseline for the hematocrit was higher for the high-dose (3.7%), compared to the low-dose group (1.9%; p=0.026, ANCOVA); and for the high-dose compared to the historical control group (0.8%; p<0.001, ANCOVA).

For the low-dose group, small within-group increases from baseline were seen for the hematocrit (1.9%; p=0.011, paired t-test), and serum ferritin (87.6 ng/ml; p=0.006, paired t-test).

For the high-dose group, small within-group increases from baseline were seen for the hematocrit (3.7%; p<0.001, paired t-test), serum iron (10.8 µg/dL; p=0.013, paired t-test), and percent iron saturation (8.3%; p<0.001, paired t-test). The serum ferritin increased by 175.1 ng/ml (p<0.001, paired t-test).

For the historical control, small within-group increases from baseline were seen for the serum iron (16.2 µg/dL; p=0.016, paired t-test), and percent iron saturation (6.1%; p=0.024, paired t-test).

Analysis of Confounding Factors on Changes in Hemoglobin and Hematocrit Values

Patients were eligible for Study 5600-01 is their EPO requirement was ≤ 10,000 units t.i.w. Twenty-two patients required changes in the EPO doses during the study (although EPO dose changes were prohibited in the study protocol). To address the effect of confounding factors on the primary efficacy variable, a statistical model was applied. This model assumed that the changes in hemoglobin and hematocrit were influenced by variations in the baseline hemoglobin value, study center, baseline EPO dose, and any change in the EPO dose during the study. The results of this model are shown below (Table 14, vol. 16, p. 126).

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Analysis of Confounding Factors on Changes in Hemoglobin and Hematocrit from Baseline through Days 40 and 60

Data Set	Efficacy Variable	End-Point	Least Square Estimates 500 mg n	500 mg LSMEAN	500 mg SE	1000 mg LSMEAN	1000 mg SE	p-values* Baseline Efficacy	Baseline rHuEPO	Center	TMT	rHuEPO Change+
Intent-to-treat Patients	HGB	Day 19	83	0.17	0.21	0.67	0.22	<0.001	0.749	0.019¶	0.006	0.421
		Day 40	83	0.36	0.20	0.94	0.22	<0.001	0.451	0.096	0.006	0.135
		Day 60	83	0.57	0.22	1.12	0.23	<0.001	0.182	0.437	0.020	0.381
	HCT	Day 19	83	0.73	0.62	2.21	0.65	<0.001	0.565	0.001¶	0.006	0.354
		Day 40	83	1.70	0.61	3.46	0.64	<0.001	0.386	0.027¶	0.005	0.251
		Day 60	83	1.81	0.66	3.31	0.68	<0.001	0.095	0.290	0.036	0.353
Stable-rHuEPO Patients	HGB	Day 19	61	0.45	0.16	0.91	0.15	<0.001	0.437	0.506	0.035	NA§
		Day 40	61	0.51	0.19	1.21	0.17	<0.001	0.228	0.522	0.005	NA
		Day 60	61	0.50	0.20	1.19	0.19	<0.001	0.123	0.687	0.011	NA
	HCT	Day 19	61	1.50	0.47	2.91	0.43	<0.001	0.244	0.194	0.025	NA
		Day 40	61	2.06	0.55	3.90	0.51	<0.001	0.137	0.236	0.013	NA
		Day 60	61	1.51	0.61	3.42	0.56	<0.001	0.031	0.993	0.020	NA

* p-values were from an ANCOVA.
+ This was categorized as: -1=decreased dose, 0=no change, and +1=increased dose.
¶ The treatment mean varied significantly across center, however, there were no significant interactions between treatment and center, so the treatment difference remained the same.
§ NA = Not Applicable.

This analysis indicated that EPO dose changes during the study had no significant effect on the change in hemoglobin or hematocrit in intent-to-treat patients (see results of the "rHuEPO Change" column).

Since the change in EPO dose had no significant effect on the change in the primary efficacy variable (hemoglobin), this factor was dropped, and the analysis was rerun without this term. Using this model, the dose of Ferrlecit was significant at each time point for both hemoglobin and hematocrit, and for both the intent-to-treat population, and the retrospectively-identified subset of patients with a stable EPO dose during the study (see the results of the "TMT" column).

A greater increase following high-dose compared to low-dose Ferrelecit was also seen (compare the results of the "Least Square Means" for low- and high-dose patients).

The baseline values for both hemoglobin and hematocrit significantly affected the hemoglobin and hematocrit outcomes at all timepoints (see results of the "Baseline Efficacy" column). In contrast, the baseline EPO dose did not significantly affect the hemoglobin and hematocrit outcomes, except for the change in hematocrit through Day 60 in stable-EPO patients (see the results of the "Baseline rHuEPO" column).

Results of the analysis of confounding factors, which included all 3 treatment groups (high-dose Ferrlecit, low-dose Ferrlecit, and the historical control) are shown below (Table 15, vol. 16, p. 130).

Analysis of Confounding Factors on Changes in Hemoglobin and Hematocrit from Baseline through Days 40 and 60

Data Set	Efficacy Variable	End-Point	Least Square Estimates: 500 mg n	500 mg LSMEAN	500 mg SE	1000 mg LSMEAN	1000 mg SE	Control LSMEAN	Control SE	p-values*: 500 vs. 1000	500 vs. Control	1000 vs. Control	Baseline Efficacy	Baseline rHuEPO	TMT	rHuEPO Change+
Intent-to-treat Patients	HGB	Day 40	107	0.29	0.19	0.92	0.20	0.18	0.27	0.002	0.662	0.003	<0.001	0.033	0.001	0.229
		Day 60	108	0.69	0.21	1.26	0.22	0.34	0.30	0.022	0.263	0.002	<0.001	0.145	0.004	0.407
	HCT	Day 40	107	1.29	0.57	3.15	0.60	0.49	0.79	0.003	0.301	<0.001	<0.001	0.011	<0.001	0.493
		Day 60	108	1.81	0.63	3.36	0.64	0.60	0.89	0.034	0.125	0.001	<0.001	0.021	0.002	0.433
Stable-rHuEPO Patients	HGB	Day 40	85	0.46	0.18	1.16	0.15	0.42	0.19	0.004	0.886	0.005	<0.001	0.035	0.003	NA#
		Day 60	86	0.57	0.21	1.29	0.18	0.33	0.23	0.012	0.460	0.002	<0.001	0.165	0.003	NA
	HCT	Day 40	85	1.74	0.52	3.53	0.45	0.94	0.56	0.011	0.300	0.001	<0.001	0.013	0.001	NA
		Day 60	86	1.46	0.63	3.38	0.54	0.38	0.66	0.022	0.248	0.001	<0.001	0.021	0.002	NA

* p-values were from an ANCOVA.
\+ This was categorized as: -1=decreased dose, 0=no change, and +1=increased dose.
\# NA = Not Applicable.

The least squares estimates of the mean changes in hemoglobin and hematocrit, adjusted by baseline efficacy value, baseline EPO dose, and change in EPO dose, were generally higher for both the low-dose and high-dose group, compared to the historical control group.

Significant differences in the mean changes in hemoglobin and hematocrit, between the high-dose compared to the low-dose, and high-dose compared to historical control were seen.

EPO dose changes had no significant effect on the change in hemoglobin or hematocrit in intent-to-treat patients (see results of the "rHuEPO Change" column); however, baseline EPO dose did (see results of "Baseline rHuEPO" column).

Because of the significant effect of baseline EPO dose noted above, Dr. Chen of the FDA Biometrics Division performed an ANCOVA analysis to compare the mean changes in hemoglobin and hematocrit, from baseline to Day 31 for Ferrlecit-treated patients, and Day 30 for historical control patients. (Note that Day 31 is the **same** as what the sponsor designated as "through Day 40" in their analyses.) The preliminary model included the treatment effect, baseline EPO dose, baseline efficacy variable, and change in EPO dose. Because the effect of changing the EPO

dose was not significant, the final model excluded the effect of changes in the EPO dose. The results are shown below (Table 2.3.1.3, Biometrics Review).

ANCOVA Analysis of Mean Changes in Hemoglobin and Hematocrit Values from Baseline to Days 31 for Ferrlecit-Treated Patients, and Day 30 for Historical Control Patients (Intent-to-Treat Population)

Variable	Treatment 500 mg (N=39)	Treatment 1000 mg (N=44)	Control (N=25)	P-value* 500 vs. 1000	P-value 500 vs. Control	P-value 1000 vs. Control
Hemoglobin(g/dL)						
n (No.of patients in analysis)	39	44	24	0.0009	0.97	0.0065
Mean	0.3	1.1	0.4			
Hematocrit (%)						
n (No.of patients in analysis)	39	44	24	0.012	0.46	0.0005
Mean	1.4	3.6	0.8			

*: P-value is associated with the ANCOVA model.

Note that significant differences in the mean changes in hemoglobin and hematocrit, between high-dose compared to low-dose Ferrlecit-treated patients, and high-dose compared to historical control patients are observed in this ANCOVA analysis, which included the covariates of treatment effect, baseline EPO dose, baseline efficacy variable, and change in EPO dose.

Safety Analysis

Extent of Exposure

A total of 88 patients received Ferrlecit in study 5600-01. Five patients discontined prematurely: one of these patients received a total of 375 mg, one patient received 125 mg, and one patient received 62.5 mg. Two patients received only the 25 mg test dose before discontinuing. Forty-four patients received a total of 1000 mg of Ferrlecit, and thirty-nine patients received a total of 500 mg.

Deaths

One patient (#109) died during the study. A narrative of this death is reproduced below (vol. 16, p. 143).

Patient #109 was a 49-year-old male with multiple illnesses and abnormalities. The patient was severely anemic (hematocrit 26%, red blood cell count 2.6 mil/cmm, hemoglobin 8.6 g/dL, ferritin 118 ng/mL, and iron saturation 12%).

Prior to starting Ferrlecit therapy (Day 10), the patient had complained of pain at the graft site used for hemodialysis access. The pre-treatment WBC count was 9000 with a shift to 75% neutrophils. The patient received Ferrlecit (62.5 mg, IV) on each of 8 consecutive hemodialysis days. He tolerated the treatment well except for occasional complaints of graft-site pain. On the day of the 7th Ferrlecit treatment, the patient reported edema of the lower extremities and a weight gain of 19 lbs from baseline (156 lbs at baseline, 175 lbs at Treatment 7).

Two days after completion of the Ferrlecit treatment (Day 19), the patient's rHuEPO was increased from 4,000 to 10,000 units because his hematocrit was still low. Liver function test values had increased, and the patient's WBC was 12,800 with 84.9% neutrophils.

Two days later, the patient was hospitalized with cellulitis of the lower extremities, left lower lobe pneumonia, volume overload, cardiomegaly, hyperkalemia, and congestive heart failure. Antibiotic therapy and supportive measures were initiated. Over the course of the following 2 weeks, the patient's condition worsened, and signs of systemic involvement were observed. Tentative diagnoses of septic phlebitis and biliary tract sepsis were considered and treated. Liver function deteriorated further, and the patient died 17 days after completion of the Ferrlecit treatment.

The chronology of events as described above is consistent with a progressive and overwhelming infectious process in a patient whose health was compromised with numerous pre-existing medical problems. The infection may have pre-dated the start of Ferrlecit therapy (75% neutrophils at baseline) and seems, in any case, to have developed independently of the Ferrlecit treatment. Systemic involvement ensued with liver function deterioration, as well as other complications. Although blood cultures were negative, the final diagnosis was sepsis.

The investigator concluded that "there does not appear to be any relation between this patient's death and his receiving Ferrlecit".

Premature Withdrawals

Five patients were prematurely withdrawn from the study, for the reasons cited below (vol. 8.1, p. 2). No further information beyond what is presented below was available from the sponsor.

Reasons for Premature Withdrawals from Study 5600-01

Patient	Reasons for Study Discontinuation
004	"Blood diarrhea"; Evaluation revealed A-V malformations that were surgically corrected. Patient discontinued following the test dose of Ferrlecit
120	"Change in mental status"; No further details provided. Patient was in the low-dsoe group, and discontinued following the 6th dose of Ferrlecit.
116	Patient withdrew after the development of pruritis and chest pain following the test dose of Ferrlecit.
311	Patient was in the high-dose group, and experienced nausea, abdominal and flank pain, fatigue, and rash following the first dose of Ferrlecit.
335	Patient was in the low-dose group, and experienced a "red, blotchy rash" following the first dose of Ferrlecit.

Serious Adverse Events

A total of 17 patients experienced a serious adverse event; none were attributed by the study investigator to study drug. All of these events resulted in hospitalization (and hence were designated as "serious"). Information provided for these cases is reproduced below (vol. 16, pp. 144-145). Note that no further information beyond what is provided below, was available from the sponsor (information amendment dated 4/6/98, vol. 10.1).

Patients who Experienced a Serious Adverse Event

Patient	Adverse Event
004 72 F	"Bloody diarrhea." Patient evaluation revealed: hemorrhoids, diverticulosis, arterio-venous malformations/corrected surgically. Patient received only a test dose of Ferrlecit.
110 77 F	Abdominal/flank pain, and shortness of breath in a patient with a pre-existing nephrolithiasis. Patient received 1000 mg of Ferrlecit.
113 61 F	Fever and cervical lymphadenopathy. Tentative diagnosis was tuberculosis. Patient received 1000 mg of Ferrlecit.
120 74 F	"Changed mental status." Patient had a history of diabetes and peripheral neuropathy, and had a R BKA. Patient received 375 mg of Ferrlecit.
121 77 M	Shortness of breath, fluid overload. Patient received 1000 mg of Ferrlecit.
122 32 M	Fever, premature ventricular contractions, fatigued for 3 weeks before event. Tentative diagnosis was viral enteritis. CMV antibodies were positive. Patient received 1000 mg of Ferrlecit.
126 81 F	Right leg pain, tingling, and discomfort, for 2 weeks. History of peripheral vascular disease and R femoral arterio-venous graft. Patient received 500 mg of Ferrlecit.
129 82 M	"Changed mental status," fever, cough. History of multi-infarct dementia and dehydration. Patient received 1000 mg of Ferrlecit.
137 78 F	Abdominal pain, melena, and diverticulosis. Patient received 1000 mg of Ferrlecit.
316 32 F	"Generalized pain." Pre-existing lupus, fibromyalgia, left leg dystrophy, and Raynaud's disease. Patient received 500 mg of Ferrlecit.
324 80 F	Right upper lobe pneumonia, weakness, dizziness, and vomiting. Patient received 500 mg of Ferrlecit.
327 87 F	Patient hospitalized for creation of arterio-venous fistula. Patient received 1000 mg of Ferrlecit.
331 45 F	Patient hospitalized for R Forearm thrombectomy. Patient received 500 mg of Ferrlecit.
332 64 M	Patient hospitalized for a ventral hernia repair and arterio-venous fistula creation. Patient received 1000 mg of Ferrlecit.
333 80 F	"Decreased level of consciousness" with tonic-clonic seizure. History of confusion for 24 hours following dialysis. EEG showed evidence of metabolic encephalopathy. Patient received 1000 mg of Ferrlecit.
338 72 M	Patient hospitalized for arterio-venous fistula creation. Patient received 1000 mg of Ferrlecit.
315 78 F	Gortex graft insertion. Collapsed vein. Patient received 1000 mg of Ferrlecit.

None of the above serious adverse events were felt by the on-site investigator to be related to study drug.

All Adverse Events

Note that safety data was not collected for historical control patients. Thus safety data was extracted from literature review articles of adverse events that have been reported in chronic hemodialysis patients. These adverse events were then proportionally distributed among the 25 historical control patients. The study report states that the review chapter to be used for this purpose was by Levin NW et. al ("Complications During Hemodialysis," in Clinical Dialysis, 2nd edition, Norwalk, Appleton, and Lange, 1990), while the table of adverse events in the "Results" section of the NDA study report states that the review article by Abuelo JG et. al., entitled, "Acute Symptoms Produced by Hemodialysis: a Review of Their Causes and Associations," (Semin Dial 1993 6 59) was used.

The incidences of adverse events were 93% in the low-dose group, 96% in the high-dose group, and 92% in the historical/literature control patients.

Individual adverse events that occurred with a frequency of ≥ 5.0% in Ferrlecit-treated patients are shown below (Tables 16 and 16a, vol. 16, pp. 137-42).

Adverse Events that Occurred with a Frequency of ≥5.0%

ADVERSE EVENT	TREATMENT GROUP		
	500 mg (N=41)	1000 mg (N=47)	Historical/Literature Control (N=25)
Body As a Whole			
Injection site reaction	15(37%)	17(36%)	-
Chest pain	1(2%)	8(17%)	9(36%)
Headache	2(5%)	7(15%)	6(24%)
Pain	5(12%)	6(13%)	-
Fatigue	3(7%)	4(9%)	-
Fever	2(5%)	2(4%)	2(8%)
Asthenia	1(2%)	5(11%)	-
Back pain	0(0%)	3(6%)	3(12%)
Abdominal pain	1(2%)	4(9%)	-
Malaise	3(7%)	1(2%)	-
Cardiovascular Disorders			
Hypotension	14(34%)	18(38%)	23(92%)
Hypertension	7(17%)	10(21%)	-
Syncope	2(5%)	4(9%)	-
Gastrointestinal Disorders			
Nausea	7(17%)	11(23%)	18(72%)
Vomiting	5(12%)	8(17%)	12(48%)
Diarrhea	1(2%)	3(6%)	-

Central and Peripheral Nervous System Disorders Cramps Dizziness Paraesthesia	17(42%) 6(15%) 4(10%)	18(38%) 9(19%) 3(6%)	17(68%) - -
Respiratory Disorders Dyspnea Upper respiratory tract infection	3(7%) 5(12%)	7(15%) 2(4%)	- -
Skin and Appendages Disorders Pruritis Itching Rash	3(7%) 0(0%) 3(7%)	4(9%) 0(0%) 1(2%)	- 7(28%) -
Metabolic and Nutritional Disorders Hyperkalemia Edema, generalized Edema, legs	5(12%) 3(7%) 4(10%)	2(4%) 3(6%) 0(0%)	- - -
Heart Rate and Rhythm Disorders Tachycardia Bradycardia	2(5%) 3(7%)	4(9%) 0(0%)	- -

Those adverse events that occurred more often in high-dose patients, by a difference of ≥ 5%, are tabulated below (Table 16 and 16a, vol. 16, pp. 137-42).

Adverse Events that Occurred More Often in High-Dose Ferrlecit Patients, By a Difference of ≥ 5%

ADVERSE EVENT	TREATMENT GROUP	
	500 mg (N=41)	1000 mg (N=47)
Body As a Whole Chest pain Headache Asthenia Back pain Abdominal pain	1(2%) 2(5%) 1(2%) 0(0%) 1(2%)	8(17%) 7(15%) 5(11%) 3(6%) 4(9%)
Gastrointestinal Disorders Nausea Vomiting	7(17%) 5(12%)	11(23%) 8(17%)
Respiratory Disorders Dyspnea	3(7%)	7(15%)

When the incidences of adverse events were statistically compared between high- and low-dose patients, only chest pain was found to occur more often in high-dose patients (p=0.033, Fisher's Exact Test); and leg edema occurred more often in low-dose patients (p=0.043, Fisher's Exact Test).

Those adverse events that were considered by the on-site Investigator to be "possibly" or "probably" related to study drug are summarized below (Appendix 13.2.3, vol. 17, pp. 31ff.).

Adverse Events Reported to be "Possibly" or "Probably" Related to Study Drug

Patient	Dose Group	Adverse Event	Severity	Relation to Study Drug
335	500mg	Rash	Severe	Possible
302	1000mg	Cramps	Mild	Possible
311	1000mg	Nausea, abdominal pain, back pain, and fatigue Rash	Moderate Mild	Probable Possible
333	1000mg	Agitation	Moderate	Possible
102	1000mg	Nausea, vomiting Syncope	Mild Moderate	Possible Possible
116	1000mg	Pruritis, Chest Pain	Moderate	Probable
117	1000mg	Parasthesia	Mild	Probable
121	1000mg	Erythrocytes Abnormal	Mild	Possible

Clinical Laboratory Evaluation

Shift table analyses of clinical laboratory parameters (which included liver function tests, complete blood count, and BUN, creatinine, and glucose values) during the study were performed (Table 18, vol. 16, pp. 154-59). Those laboratory values for which > 5% of patients were in the "normal→abnormal" category at Day 19 compared to baseline, are tabulated below (Appendix 13.2.5, vol. 17, p. 64ff.).

Laboratory Values for Which > 5% of Patients had a Normal Value at Baseline, and an Abnormal Value at Day 19

Laboratory Parameter	500 mg (N=41)	1000 mg (N=47)	Comments
Glucose	2(5%)	6(13%)	For the high-dose group, 6% of patients at Day 31, and 13% of patients at Day 47, had persistently abnormal glucose values. Abnormal glucose values were generally non-significant increases, except for patient #107 (high-dose group) who increased from 150 mg/dL at baseline to 586, 527, and 495 mg/dL, at Days 19, 31, and 47, respectively.
WBC	4(10%)	4(9%)	For the high-dose group, 11% of patients at Day 31, and 4% of patients at Day 47 had persistently abnormal WBC values. No WBC value was > 15K/mm3.
Lymphocytes	2(5%)	5(11%)	For the high-dose group, 2% of patients at Days 31 and 47, had persistently abnormal lymphocyte values.
Neutrophils	3(7%)	5(11%)	For the high-dose group, 2% of patients at Day 31, and 4% of patients at Day 47, had persistently abnormal neutrophil values.

There was no laboratory value for which > 4% of patients (where 4% = 1 patient out of a total of 25 historical control patients), were in the "normal→abnormal" category, at Day 19 compared to baseline.

For comparison, baseline laboratory values from a population of approximately 1100 hemodialysis patients were obtained from the NIDDK Hemodialysis Study, Data Coordinating Center, (Cleveland Clinic Foundation). These values are summarized below (Table 20, vol. 16, p. 163).

Summary of Baseline Laboratory Values for Hemodialysis Patients from the NIDDK Hemodialysis Study

TEST	Patients Evaluated	NORMAL		ABNORMAL LOW		ABNORMAL HIGH		TOTAL		Range	
		N	%	N	%	N	%	N	%	Lower limit	Upper limit
ALK PHOS	1118	583	52.15	2	0.18	533	47.67	535	47.85	33.00	99.00
ALT	1086	1023	94.20	20	1.84	43	3.96	63	5.80	5.00	55.00
AST	1067	949	88.94	26	2.44	92	8.62	118	11.06	7.00	48.00
BILIRUBIN	1113	1103	99.10	0	0.00	10	0.90	10	0.90	0.10	1.60
CREATININE	1132	0	0.00	0	0.00	1132	100.0	1132	100.00	0.80	1.40
GLUCOSE	1120	576	51.43	34	3.04	510	45.54	544	48.57	65.00	120.00
WBC	1089	963	88.51	71	6.53	54	4.96	125	11.47	4000.00	11000.00

Source: NIDDK Hemodialysis Study, Data Coordinating Center, The Cleveland Clinic Foundation, Cleveland, OH 44195.

Baseline creatinine values were always abnormally high, while half the values for glucose and alkaline phosphatase were abnormally high; the other half were normal.

Vital Signs

No clinically significant effects on vital signs were reported.

BEST POSSIBLE

STUDY 5600-03

Study 5600-03 was a single-center, non-randomized, open-label, historically-controlled, variable-dose, compassionate-use study of the safety and efficacy of Ferrlecit in iron-deficient hemodialysis patients. The primary efficacy variable was the change in hemoglobin from baseline to the last available observation through Day 50. The study period was from 5/28/94 through 4/2/96.

The principal investigator, Dr. Bernard Haberstroh, of the Kitchener Waterloo Health Center in Ontario, Canada, initially began treating patients with Ferrlecit under the Canadian compassionate-use IND [redacted] Eligible patients under this IND included non-hemodialysis patients, including patients who were receiving hemodialysis for acute renal failure, patients who were on peritoneal dialysis, and patients who had been previously been exposed to Ferrlecit. Further, the total dose of drug administered depended on the protocol under which the patient had entered the study, the availability of the study drug to the investigator, and the clinical judgement of the investigator. Thus, patients who did not meet the entry criteria of Study 5600-01 were retrospectively excluded from the analyses of this study. Further, all ~~patients~~ who met the entry criteria of Study 5600-01 and received ANY Ferrlecit, were included in the Ferrlecit-treatment group, regardless of the actual dose of Ferrlecit received.

Inclusion criteria were:

- age greater than 18 years
- ferritin level below 100 ng/mL or iron saturation below 18%
- hemoglobin below 10 g/dL or hematocrit ≤ 32%
- patients on long-term hemodialysis

Exclusion criteria were:

- patients with unstable/uncontrolled pulmonary, cardiovascular, hepatic, endocrine, neuro-psychiatric, infectious, immunologic, or malignant disorders
- HIV and/or hepatitis B Surface Antigen positivity
- women who are pregnant, or of child-bearing potential
- use of parenteral iron (including RBC transfusions) and/or investigational drugs which may interfere with iron metabolism within the previous 2 months
- EPO requirement of > 10,000 units ≥ t.i.w.

Note that the above inclusion and exclusion criteria are identical to those of Study 5600-01 (including protocol amendments).

All patients were to receive a 25 mg test dose of Ferrlecit, administered over 1 hour during hemodialysis on Study Day -5. If the test dose was tolerated, Ferrlecit in quantities of 62.5 mg(1 ampule) or 125 mg (2 ampules) diluted in 100 ml of normal saline, were to be administered intravenously over 1 hour at subsequent, consecutive dialysis sessions. The investigator determined the number of doses to be given.

The primary efficacy variable was the change in hemoglobin from baseline to endpoint (last available observation through Day 50). Secondary efficacy variables were changes from baseline of the hematocrit, percent iron saturation, serum ferritin, serum iron, and mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC).

The study schedule is reproduced below (vol. 20, p. 17).

	Study Days (Treatment/Hemodialysis Days)												
	-14 to -7	-5 (test dose)	1 (1)	3 (2)	5 (3)	8 (4)	10 (5)	12 (6)	15 (7)	17 (8)	19	31*	47*
Informed Consent	x												
HIV, hepatitis, pregnancy tests	x												
Hematology#	x										x	x	x
Hepatic/Renal Labs $	x										x	x	x
AEs		x	x	x	x	x	x	x	x	x	x		
Clinical Evaluation**	x	x	x	x	x	x	x	x	x	x	x	x	x

* 2 weeks after treatment.
+ 1 month after treatment.
# Hematology tests: Hemoglobin, hematocrit, MCV, MCH, MCHC, serum iron, % iron saturation, serum ferritin, WBC count, differential, RBC count, reticulocyte count, and platelet count.
$ Hepatic/renal Chemistry tests: ALT, AST, bilirubin, alkaline phosphatase, BUN, creatinine, and glucose.
** Includes measurements of blood pressure, pulse, temperature, and weight.

Sixty-three patients were evaluated in this study: 38 in the Ferrlecit-treated group, and 25 patients in the historical control group.

STUDY RESULTS

Patient Disposition

Sixty-three patients were evaluated in this study: 38 in the Ferrlecit-treated group, and 25 patients in the historical control group.

Ferrlecit-treated patients were considered to have completed the study per protocol, if they received at least 8 doses of study medication. A total of 14(37%) of completed the study per protocol. Twelve (32%) Ferrlecit-treated patients received less than 8 doses, and 12(32%) patients had incomplete dosing information, so that the number of Ferrlecit doses could not be determined.

A list of the number of (known) Ferrlecit doses received, including total Ferrlecit dose, is shown below (vol. 10.1, p. 5).

Ferrlecit Received by Patients in Study 5600-03

Patient Number	Number of Doses Received	Total Dose (mg)
511	8	500
534	8	500
545	8	1000
549	8	1000
586	8	500
502	5	312.5
526	7	875
539	3	187.5
543	7	875
544	3	375
547	5	625
548	5	625
551	3	375
552	1	125
556	5	625
559	1	62.5
566	5	625

Note that only 5(13%) patients are listed as having received 8 doses of Ferrlecit.

Data on EPO dosage was available for 31 Ferrlecit-treated patients. Most patients received a mean of 4000-6000 units of EPO, with the exceptions of patients #502 and #530, who received 8000 units; patient #538, who received 10,000 units; and patient #556, who received 2000 units (vol. 10.1, Attachment A).

Protocol Deviations

Not all patients received Ferrlecit at consecutive dialysis sessions.

Many Ferrlecit-treated patients received oral iron supplementation during the study.

Demographics and Other Baseline Variables

A summary of patient demographics and other baseline variables is shown below (vol. 20, p. 29-30).

Patient Baseline Demographics and Hemoglobin Values

Variable	Treatment Group: Ferrlecit (N = 38)	Treatment Group: Control (N = 25)	p-value*
Age (yrs)			
n	37	25	0.429
Mean (Std)	55.5 (15.5)	52.2 (16.6)	
Min	22.0	21.0	
Max	84.0	84.0	
Age category (n %)			
Female: age≤51	6 (16.2)	8 (32.0)	0.024
Female: 51<age≤65	1 (2.7)	6 (24.0)	
Female: age>65	6 (16.2)	3 (12.0)	
Male: age≤65	20 (54.1)	6 (24.0)	
Male: age>65	4 (10.8)	2 (8.0)	
Gender (n %)			
Female	14 (36.8)	17 (68.0)	0.021
Male	24 (63.2)	8 (32.0)	
Race (n %)			
White	36 (94.7)	10 (40.0)	<0.001
Black	0 (0.0)	8 (32.0)	
Asian	2 (5.3)	1 (4.0)	
Hispanic	0 (0.0)	5 (20.0)	
Unknown	0 (0.0)	1 (4.0)	
Weight (lbs)			
n	34	23	0.012
Mean (Std)	170.9 (42.9)	143.6 (35.9)	
Min	86.3	83.0	
Max	272.9	222.7	
Systolic BP (mmHg)			
n	34	13	0.001
Mean (Std)	168.6 (17.0)	170.0 (19.0)	
Min	118.0	139.0	
Max	198.0	199.0	
Diastolic BP (mmHg)			
n	34	13	0.001
Mean (Std)	94.4 (11.4)	86.6 (16.2)	
Min	57.0	61.0	
Max	111.0	112.0	
Pulse (bpm)			
n	34	12	0.054
Mean (Std)	90.0 (17.6)	78.9 (13.1)	
Min	53.0	56.0	
Max	140.0	96.0	
Temperature (°C)			
n	26	-	NA†
Mean (Std)	36.5 (0.6)		
Min	35.0		
Max	37.5		
Baseline Hemoglobin (g/dL)			
n	38	25	0.263
Mean (Std)	9.1 (0.9)	9.4 (0.8)	
Min	7.5	7.8	
Max	11.5	10.4	

* For a continuous variable, an ANOVA model with effects for treatment group was used to compare the group means, and the p-value was associated with the F test. For a categorical variable, the p-value was associated with the Fisher's Exact Test.
† - = No data available.
‡ NA = Not Applicable.

No significant difference in the baseline hemoglobin was seen between Ferrlecit- and historical control patients. Overall the Ferrlecit-treated group was comprised of more of the following: males, males of age ≤ 65 years, and Caucasians. The mean weight of Ferrlecit-treated patients was 180 kg, compared to a mean weight of 144 kg in historical control patients.

A summary of the baseline parameters of hematocrit, serum iron, percent iron saturation, serum ferritin, and red blood cell indices, is shown below (vol. 20, p. 31).

Baseline Hematocrit, Iron Studies, and RBC Indices

	Treatment Group		
Variable	Ferrlecit (N = 38)	Control (N = 25)	p-value*
Baseline Hematocrit (%)			
n	38	25	0.050
Mean (Std)	27.3 (2.8)	28.6 (2.1)	
Min	21.5	24.0	
Max	34.8	31.4	
Baseline Percent Iron Saturation (%)			
n	37	25	0.001
Mean (Std)	9.8 (5.5)	14.2 (4.4)	
Min	4.0	6.7	
Max	30.0	27.3	
Baseline Serum Ferritin (ng/mL)			
n	37	12	<0.001
Mean (Std)	76.6 (78.0)	605.6 (390.9)	
Min	6.0	41.0	
Max	353.0	1000	
Baseline Serum Iron (ug/dL)			
n	37	25	0.147
Mean (Std)	27.0 (19.1)	33.5 (13.6)	
Min	5.6	16.0	
Max	111.7	81.0	
Baseline MCH (pg)			
n	38	25	<0.001
Mean (Std)	28.2 (2.8)	31.4 (3.3)	
Min	23.2	26.6	
Max	34.0	39.1	
Baseline MCV (fl)			
n	38	25	<0.001
Mean (Std)	84.3 (7.2)	96.0 (9.0)	
Min	71.9	84.6	
Max	99.5	116.7	
Baseline MCHC (g/dL)			
n	24	25	0.016
Mean (Std)	33.3 (0.9)	32.7 (0.6)	
Min	31.2	31.4	
Max	34.8	34.2	

* For a continuous variable, an ANOVA model with effects for treatment group was used to compare the group means, and the p-value was associated with the F test. For a categorical variable, the p-value was associated with the Fisher's Exact Test.

Notably higher baseline values in historical control patients included serum ferritin (606 ng/ml in historical control, compared to 77 ng/ml in Ferrlecit-treated pateints), and MCV values (96 fl in historical control, compared to 84 fl in Ferrlecit-treated patients).

Efficacy Analysis

Mean Change in Hemoglobin

The primary efficacy variable was the change in hemoglobin from baseline to endpoint (last available observation through Day 50). For the historical control group, the endpoint was defined as the last available observation through Day 60. These data were analyzed by an ANCOVA model, which included the factors of treatment group, baseline hemoglobin level, and their interaction. If the interaction was not significant, the analysis was rerun, and a model that did not include the interaction term was used. The significance of the mean change from baseline to endpoint for each dose group was determined using a paired t-test.

The results of the ANCOVA analysis for mean change in hemoglobin is shown below (Table 4, vol. 20, p. 33).

Mean Change in Hemoglobin
ANCOVA Analysis

	Treatment Group		
Variable	Ferrlecit (N = 38)	Control (N = 25)	p-value*
Hemoglobin (g/dL)			
n	38	25	0.022
Mean	1.3	0.4	
Std	1.3	1.3	
Min	-1.2	-2.6	
Max	4.1	2.7	
c.i.	(0.9, 1.6)	(-0.0, 0.9)	
Probt+	<0.001	0.136	

* p-value is associated with the ANCOVA.
\+ p-value is associated with the paired t-test.

The mean change in hemoglobin from baseline to endpoint was greater for Ferrlecit-treated (1.3 g/dL through Day 50), compared to historical control (0.4 g/dL through Day 60) patients (p=0.022, ANCOVA).

The within-group changes in hemoglobin from baseline were statistically significant for Ferrlecit-treated (p<0.001, paired t-test), but not historical control patients (p=0.136, paired t-test).

Mean Changes in Hematocrit, Iron Studies, and Red Blood Cell Indices

The results of the ANCOVA analyses of changes in hematocrit, iron studies, and red blood cell indices, from baseline to the last available observation through Day 50 for the Ferrlecit-treated group, and through Day 60 for the historical control group, are shown below (Table 5, vol. 20, pp. 34-5).

Mean Changes in Hematocrit, Iron Studies, and Red Blood Cell Indices
Results of ANCOVA Analysis

Variable	Treatment Group: Ferrlecit (N = 38)	Treatment Group: Control (N = 25)	p-value*
Hematocrit (%)			
n	38	25	0.002
Mean	3.8	0.2	
Std	3.6	3.7	
Min	-3.7	-7.2	
Max	11.2	6.6	
c.i.	(2.9, 4.8)	(-1.0, 1.5)	
Probt+	<0.001	0.758	
Percent Iron Saturation (%)			
n	37	25	0.101
Mean	6.7	1.7	
Std	7.2	6.4	
Min	-12.0	-7.2	
Max	22.0	15.3	
c.i.	(4.7, 8.7)	(-0.4, 3.9)	
Probt+	<0.001	0.107	
Serum Ferritin (ng/mL)			
n	37	2	0.580
Mean	72.9	-145	
Std	116.0	205.1	
Min	-168	-290	
Max	504.0	0.0	
c.i.	(40.7, 105.1)	(-1060,770.5)	
Probt+	0.001	0.500	
Serum Iron (ug/dL)			
n	37	25	0.358
Mean	11.5	3.7	
Std	21.1	14.7	
Min	-67.0	-18.0	
Max	61.4	44.0	
c.i.	(5.6, 17.3)	(-1.3, 8.7)	
Probt+	0.002	0.222	
MCH (pg)			
n	38	25	0.070
Mean	0.9	-0.4	
Std	1.0	1.8	
Min	-0.5	-6.7	
Max	4.6	2.5	
c.i.	(0.6, 1.1)	(-1.0, 0.3)	
Probt+	<0.001	0.336	
MCV (fl)			
n	38	25	<0.001
Mean	2.4	-3.4	
Std	2.4	4.5	
Min	-2.4	-22.8	
Max	10.8	-0.1	
c.i.	(1.7, 3.1)	(-5.0, -1.9)	
Probt+	<0.001	0.001	
MCHC (g/dL)			
n	24	25	0.021
Mean	0.0	0.8	
Std	0.6	0.9	
Min	-1.2	-0.9	
Max	1.3	2.9	
c.i.	(-0.2, 0.3)	(0.5, 1.1)	
Probt+	0.766	<0.001	

* p-value is associated with the

A small increase in the hematocrit from baseline was observed for Ferrlecit-treated patients (3.8%; p<0.001, paired t-test). The mean change from baseline for the hematocrit was greater for Ferrlecit-treated patients (3.8%), compared to historical control patients (0.2%; p=0.002, ANCOVA).

No significant effect of age or race on the treatment mean, or treatment difference in hemoglogin or hematocrit were reported. A significant treatment-by-gender interaction was noted for female patients however: females in the Ferrlicit-treated group had significantly greater increases in hemoglobin and hematocrit, than females in the historical control group).

Changes in hemoglobin were not significantly affected by baseline EPO doses (vol. 20, p. 38).

A summary table of the efficacy outcomes for the intent-to-treat population of study 5600-01, and patients treated in study 5600-03, is shown below.

Comparison of the Changes in Efficacy Variables for Studies 5600-01 and 5600-03

	Study 5600-01			Study 5600-03		
	High-dose Ferrlecit (1000 mg) Day 40	Hist Control Day 40	Absolute Difference	Variable-dose Ferrlecit (≤1000 mg) Day 50	Hist Control Day 60	Absolute Difference
Hb (g/dL)	1.1	0.4	0.7	1.3	0.4	0.9
Hct (%)	3.6	0.8	2.8	3.8	0.2	3.6
Fe (µg/dL)	11.7	16.2	-4.5	11.5	3.7	7.8
Iron Saturation(%)	8.5	6.1	2.4	6.7	1.7	5.0
Ferritin (ng/mL)	199	N.D.	-	72.9	-145	218

Note that the magnitude of changes in efficacy variables for high-dose Ferrlecit patients in study 5600-01 **through Day 40** (actually measured on Day 31), are similar to those for variable-dose Ferrlecit patients in study 5600-03 **through Day 50** (actually measured on Day 50), except for the serum ferritin value. Also note that iron study values in historical control patients decrease with time (i.e. compare Day 60 with Day 40 results), so that there was a (suggestive) trend toward greater differences between treatment groups at later timepoints.

Summary of Study 5600-03

In summary, interpretation of the results of Study 5600-03 is limited by the fact that this study was a small, single-center, compassionate-use, variable-dose, historically-controlled trial. However, the results of study 5600-03 corroborate the results of study 5600-01, and thus support the efficacy of Ferrlecit for iron replacement therapy in chronic hemodialysis patients.

Safety Analysis

Extent of Exposure

As per vol. 20, p. 40: "This was a variable dose study; the maximum amount of Ferrlecit received during the treatment course by any patient was 1125 mg, and the minimum amount was 62.5 mg."

Deaths

There were no deaths in Study 5600-03.

Premature Discontinuations

One patient (#552) discontinued due to dizziness, lightheadedness, diplopia, malaise, and weakness, considered by the investigator to be "probably" related to study drug. This patient had received a total of 125 mg of Ferrlecit. No further information was provided.

Serious Adverse Events

A total of 4 patients were hospitalized for the following (serious) adverse events. Available information on these cases is reproduced below (vol. 20, p. 44).

Serious Adverse Events

Patient Number	Age	Sex	Event	Relation to study drug
536	38	M	Rigors and chills. Blood cultures showed *Staphylococcus aureus* bacteremia. Received 1000 mg Ferrlecit.	None
538	68	M	Myocardial infarction. One dose of Ferrlecit was withheld. Received 1125 mg Ferrlecit.	None
544	35	M	Chills. Four blood cultures showed *Staphylococcus* epidermis bacteremia. Received 375 mg Ferrlecit.	Unlikely
552	65	M	Dizziness, lightheadedness, diplopia, malaise, and weakness. Received 125 mg Ferrlecit.	Probable

All Adverse Events

Note that safety data was not collected for historical control patients. Instead, safety data was extracted from a literature review article by Abuelo et. al. (Semin Dial 1993 6 59). These adverse events were then proportionally distributed among the 25 historical control patients.

A total of 74% of Ferrlecit-treated patients experienced an adverse event, and these are summarized below (Table 8, vol. 20, pp. 42-3).

All Adverse Events

BODY SYSTEM Adverse Event	Ferrlecit (N = 38) n	%	Control* (N = 25) n	%
ANY BODY SYSTEM	28	73.7	23	92.0
BODY AS A WHOLE	17	44.7	9	36.0
Chest Pain	4	10.5	9	36.0
Headache	0	0.0	6	24.0
Chills	3	7.9	2	8.0
Fever	2	5.3	2	8.0
Asthenia	3	7.9	-	
Abscess	3	7.9	-	
Pain Back	0	0.0	3	12.0
Abdominal Pain	3	7.9	-	
Carcinoma	2	5.3	-	
Sepsis	2	5.3	-	
Pain	2	5.3	-	
Infection	2	5.3	-	
Flu Syndrome	1	2.6	-	
Malaise	1	2.6	-	
CARDIOVASCULAR DISORDERS	4	10.5	23	92.0
Hypotension	4	10.5	23	92.0
GASTRO-INTESTINAL DISORDERS	8	21.1	18	72.0
Nausea	2	5.3	18	72.0
Vomiting	4	10.5	12	48.0
Diarrhea	3	7.9	-	
Nausea and Vomiting	1	2.6	-	
Nausea Vomiting and Diarrhea	1	2.6	-	
Dyspepsia	1	2.6	-	
AUTONOMIC NERVOUS	0	0.0	17	68.0
Muscle Cramp	0	0.0	17	68.0
Restlessness	0	0.0	6	24.0
SKIN AND APPENDAGES	11	28.9	-	
Application Site Reaction	10	26.3	-	
Skin Carcinoma	1	2.6	-	
DIGESTIVE SYSTEM	6	15.8	-	
Gastrointestinal Disorder	2	5.3	-	
Rectal Disorder	2	5.3	-	
Large Intestine Perforation	1	2.6	-	
Gastrointestinal Hemorrhage	1	2.6	-	
Gastroenteritis	1	2.6	-	
Anorexia	1	2.6	-	

CARDIOVASCULAR SYSTEM	4 (10.5)	-
Myocardial Infarct	2 (5.3)	-
Syncope	1 (2.6)	-
Atrial Fibrillation	1 (2.6)	-
Angina Pectoris	1 (2.6)	-
SKIN AND APPENDAGES DISORDERS	0 (0.0)	7 (28.0)
Itching	0 (0.0)	7 (28.0)
MUSCULOSKELETAL SYSTEM	7 (18.4)	-
Leg Cramps	3 (7.9)	-
Arthralgia	2 (5.3)	-
Tenosynovitis	1 (2.6)	-
Myalgia	1 (2.6)	-
Arthritis	1 (2.6)	-
RESPIRATORY SYSTEM	5 (13.2)	-
Dyspnea	4 (10.5)	-
Lung Edema	1 (2.6)	-
Cough Increased	1 (2.6)	-
NERVOUS SYSTEM	5 (13.2)	-
Dizziness	2 (5.3)	-
Insomnia	1 (2.6)	-
Hypesthesia	1 (2.6)	-
Depersonalization	1 (2.6)	-
Agitation	1 (2.6)	-
METABOLIC AND NUTRITIONAL DISORDERS	2 (5.3)	-
Hypoglycemia	1 (2.6)	-
Hypervolemia	1 (2.6)	-
SPECIAL SENSES	2 (5.3)	-
Diplopia	1 (2.6)	-
Abnormal Vision	1 (2.6)	-
HEMIC AND LYMPHATIC SYSTEM	1 (2.6)	-
Hypochromic Anemia	1 (2.6)	-

* Historical control data taken from Abeuelo et al. (54).
\+ - = No data available.

Adverse events that were reported by the on-site Investigator to be "possibly" or "probably" related to Ferrlecit were: dizziness, diplopia, malaise, and asthenia in one patient; and diarrhea, myalgia, and arthralgia in a second patient.

Clinical Laboratory Evaluation

Shift table analyses of clinical laboratory parameters (which included liver function tests, complete blood count, and BUN, creatinine, and glucose values) during the study were performed (Table 10, vol. 20, pp. 50-1). Those laboratory values for which ≥ 5% of patients were in the "normal→abnormal" category at Day 50 compared to baseline, were: glucose (5/38 patients or 13%), and WBC (2/38 patients or 5%). No information was recorded for bilirubin or neutrophil values.

For comparison, baseline laboratory values from a population of approximately 1100 hemodialysis patients were obtained from the NIDDK Hemodialysis Study, Data Coordinating Center, (Cleveland Clinic Foundation). These values are summarized below (Table 20, vol. 16, p. 163).

Summary of Baseline Laboratory Values for Hemodialysis Patients from the NIDDK Hemodialysis Study

TEST	Patients Evaluated	NORMAL N	NORMAL %	ABNORMAL LOW N	ABNORMAL LOW %	ABNORMAL HIGH N	ABNORMAL HIGH %	TOTAL N	TOTAL %	Range Lower Limit	Range Upper Limit
ALK PHOS	1118	583	52.15	2	0.18	533	47.67	535	47.85	33.00	99.00
ALT	1086	1023	94.20	20	1.84	43	3.96	63	5.80	5.00	55.00
AST	1067	949	88.94	26	2.44	92	8.62	118	11.06	7.00	49.00
BILIRUBIN	1113	1103	99.10	0	0.00	10	0.90	10	0.90	0.10	1.60
CREATININE	1132	0	0.00	0	0.00	1132	100.0	1132	100.00	0.80	1.40
GLUCOSE	1120	576	51.43	34	3.04	510	45.54	544	48.57	65.00	120.00
WBC	1088	952	88.51	71	6.53	54	4.96	125	11.48	4000.00	11000.00

Source: NIDDK Hemodialysis Study, Data Coordinating Center, The Cleveland Clinic Foundation, Cleveland, OH 44195.

Baseline creatinine values were always abnormally high, while half the values for glucose and alkaline phosphatase were abnormally high; the other half were normal. Approximately 11% of WBC values were also abnormal.

Vital Signs

No clinically significant effects on vital signs (from baseline through Day 50) were reported.

OTHER STUDIES TO SUPPORT THE EFFICACY OF FERRLECIT

Published Reports

Five published reports were submitted to support the efficacy of Ferrlecit in treating iron deficiency in chronic hemodialysis patients. These studies are discussed below.

Navarro JF, et. al., "Effectiveness of Intravenous Administration of Fe-Gluconate-Na Complex to Maintain Adequate Body Iron Stores in Hemodialysis Patients," Am J Neph 1996 16 268

This 6-month study prospectively examined the effects of the monthly administration of 62.5 mg of sodium ferric gluconate, on body iron stores in chronic hemodialysis patients.

Fifty-eight patients were enrolled; 31 of these patients were excluded for the following reasons: chronic hepatitis (n=8), chronic inflammatory diseases (n=2), intercurrent infection during the follow-up period (n=4), external blood losses (n=5), red blood cell transfusion requirement (n=6), and variations of the monthly hemoglobin of ≥ 1 g/dL (n=6).

Of the 27 remaining evaluable patients; half were female, the mean age was 57 years, and all were on hemodialysis for more than 2 years. Sixteen (60%) patients were on a stable EPO maintenance doses.

Study drug was administered monthly, as 62.5 mg in 50 ml of saline, given over 30 minutes at the end of dialysis.

The results are shown below (vol. 25, p. 194). Note that "iron stores" in the table below was calculated from the modified formula of Cook et. al. (Nephrol Dial Transplant 1993 8 846): iron stores (in mg) = 400 x ln (serum ferritin in mg/L ÷ 50)

Parameter	Basal	Time, months		
		2	4	6
Hemoglobin, g/dl	10.7±1.1	10.7±1.2	10.7±1.2	10.6±1
Hematocrit, %	32.8±3.8	32.8±4.5	32.5±3.9	32.3±3
Ferritin, µg/l	187±96	203±96	230±120	196±115
Iron stores, mg	457±273	461±205	470±199	451±316

p = NS for all parameters.

No significant differences in hemoglobin, hematocrit, ferritin, or (calculated) iron store values from baseline, were observed. No allergic or other adverse events were reported.

Taylor JE, et. al., "Regular low-dose intravenous iron therapy improves response to erythropoietin in hemodialysis patients," (Nephrol Dial Transplant 1996 11 1079)

In this 6-month study, 46 stable hemodialysis patients were treated with 62.5 mg of sodium ferric gluconate post-dialysis; twice-weekly, weekly, or every two weeks, depending on their serum ferritin levels. The effects on hemoglobin, serum ferritin, EPO dose, and iron dose were determined.

Of the 46 hemodialysis patients who participated in this study, 67% were male, and the median age was 67 years. All patients had received EPO for at least 6 months, with a stable EPO dose for at least 3 months. Patients were excluded for infection, malignancy, liver disease, or chronic inflammation. All patients had ferritin levels of < 600 µg/L, had not received a blood transfusion in the preceding 6 months, were taking oral iron, and had not received intravenous iron in the previous 3 months.

Patients were administered 62.5 mg of intravenous ferric gluconate twice weekly (for a ferritin of < 100 µg/L), weekly (for a ferritin of 100-250 µg/L), or every two weeks (for a ferritin of 250-600 µg/L). Study medication was given as a slow injection through the fistula needle at the end of dialysis. Oral iron supplements were discontinued. EPO doses were adjusted up or down by 30-50%, in order to maintain hemoglobin levels of 11-13 g/dL for male patients, and 10-12 g/dL for female patients.

Changes in hemoglobin, ferritin, EPO dose, and Ferric Gluconate dose over a 6-month period, in 34 patients with an initial ferritin of > 100 µg/L, are summarized below:

Changes in hemoglobin, ferritin, EPO dose, and Ferric Gluconate Dose for Patients with an Initial Ferritin of > 100 µg/L

	Pre haemoglobin (g/dl)	Post haemoglobin (g/dl)	Pre ferritin (µg/l)	Post ferritin (µg/l)	Pre erythropoietin (× 1000 i.u./wk)	Post erythropoietin (× 1000 i.u./wk)	Pre iron (ml/wk)	Post iron (ml/wk)
Median	9.85	11.25	176	304.5	6	4	5	2.5
Range	6.5–12.8	9.9–13.3	103–519	121–792	3–15	0–15	2.5–10	0–5
P		<0.0001		<0.0001		0.005		<0.0001

The mean hemoglobin increased from 9.8 g/dL to 11.3 g/dL. Mean EPO requirements decreased from 6000 U/week to 4000 U/week (Note that EPO doses were adjusted to maintain hemoglobin values in a prespecified range.) Mean Ferric Gluconate requirements decreased from 62.5 mg/week, to 31.25 mg /week.

Changes in hemoglobin, ferritin, EPO dose, and Ferric Gluconate dose over a 6-month period, in 12 patients with an initial ferritin of < 100 µg/L, are summarized below:

Changes in hemoglobin, ferritin, EPO dose, and Ferric Gluconate Dose for Patients with an Initial Ferritin of < 100 µg/L

	Pre haemoglobin (g/dl)	Post haemoglobin (g/dl)	Pre ferritin (µg/l)	Post ferritin (µg/l)	Pre erythropoietin (× 1000 i.u./wk)	Post erythropoietin (× 1000 i.u./wk)	Pre iron (ml/wk)	Post iron (ml/wk)
Median	10.05	11.00	68	210.5	9	6	10	2.5
Range	8.2–11.9	9.9–11.9	20–96	91–447	4–30	2–10	5–10	1.25–10
P		0.03		0.003		0.05		0.005

The mean hemoglobin increased from 10.1 g/dL to 11.0 g/dL. Mean EPO requirements decreased from 9000 U/week to 6000 U/week (Note that EPO doses were adjusted to maintain hemoglobin values in a prespecified range.) Mean Ferric Gluconate requirements decreased from 125 mg/week, to 31.25 mg/week.

No adverse events were reported in this study.

Pascual J, et. al., "Sodium ferric gluconate complex given intravenously for iron deficiency in hemodialysis," Clin Nephrol 1991 35 87

In a letter to the editor, Pascual J, et. al., reported the results of the administration of 1 gram of sodium ferric gluconate as 8 divided doses by slow i.v. injection to chronic hemodialysis patients. A total of 19 patients, of mean age 50 years, were stratified into the following 3 groups: **Group I** - 8 patients with iron deficiency anemia; **Group II** - 6 patients with anemia, iron deficiency, and concomitant treatment with nandrolone decanoate, and **Group III** - 5 patients with iron deficiency with a poor response to EPO. Results for hemoglobin (Hb) and serum ferritin (SF) values are shown below:

Group		Before i.v. iron	After i.v. iron***: 1 month	3 months	6 months
I	Hb (g/dl)*	7.7 ± 0.6	8.4 ± 0.9	8.9 ± 1.3	8.6 ± 1.3
	SF (µg/l)**	23 (14–48)	149 (67–263)	163 (107–561)	111 (98–329)
II	Hb (g/dl)*	8.4 ± 1.6	8.8 ± 0.8	9.3 ± 2.4	9.6 ± 1.3
	SF (µg/l)**	28 (17–37)	130 (45–264)	231 (174–370)	199 (151–392)
III	Hb (g/dl)*	8.5 ± 1.4	10.7 ± 2.5	11.2 ± 1.6	10.3 ± 2.7
	SF (µg/l)**	26 (20–39)	193 (58–1040)	213 (80–298)	154 (115–927)

* = Arithmetic mean ± SD, ** = Geometric means (range), *** = All values higher with respect to basal ones ($p < 0.05$, paired t-test)

Increases in hemoglobin were seen for all three groups, with the greatest increase in Group III patients. Serum ferritin increased in all groups up to 3 months, then declined. The authors concluded that "iron deficiency will become an increasing problem as erythropoietin is used more widely, unless prophylactic iron is administered i.v. when serum ferritin falls below adequate levels."

No adverse events were reported.

Pascual J, et. al., "Intravenous Fe-Gluconate-Na for Iron-Deficient Patients on Hemodialysis," Nephron 1992 60 121

In a letter to the editor, Pascual J, et. al. reported the results of a total of 59 hemodialysis patients with a baseline serum ferritin of < 50 ng/ml, treated with 1 gram of Ferrlecit, given as 8 divided doses. The results of the first 19 of these patients was described in a publication by Pascual J et. al. (discussed above).

Forty additional patients completed 6 months of follow-up: **Group I** - 18 patients with iron-deficiency anemia, **Group II** - 10 patients with iron-deficiency anemia and concomitant nandrolone decanoate therapy, and **Group III** - 12 patients with iron-deficiency anemia associated with erythropoietin therapy. The results are shown below:

	Group I	Group II	Group III
Sex (M/F)	9/9	7/3	6/6
Age, years	56±12	58±7	43±15
Time on HD, months	41±12	87±36	71±48
Hemoglobin, g/dl			
Basal	8.7±1.5	8.7±1.8	9.4±1.6
3 months*	10±1.6	10.8±2.7	11±1.4
6 months*	9.9±1.7	10.2±2	9.8±1.7
Serum ferritin, ng/ml			
Basal	27±1	29±1	27±1
1 month**	135±2	187±1	167±2
3 months**	143±2	163±2	199±2
6 months**	108±2	113±2	149±2
Positive responses	15/18	10/10	11/12

All values are expressed as arithmetic mean±SD except for serum ferritin (geometric mean±SD of log).
* $p < 0.05$ with respect to controls (paired t test).
** $p < 0.01$ with respect to basal values (paired t test).

Hemoglobin and serum ferritin increased in all groups up to 3 months, then began to decrease. The authors concluded that, "we obtained excellent repletion of iron stores and increased hemoglobin with (Ferrlecit) in our severely iron-deficient population."

Three patients experienced serious adverse events in this study, and are described below (Nephrol Dial Transplant 1992 7 271):

A 36 year-old male hemodialysis patient had a hemoglobin of 6.7 g/dL and serum ferritin of 53 ng/ml; he was given i.v. ferric gluconate (1 gram divided into 8 post-hemodialysis doses). A few minutes after the first slow injection of 125 mg, he experienced malaise, heat, vomiting, and loin pain, lasting 5-6 minutes. No hypotension was noted. After the next dialysis session, another i.v. ferric gluconate infusion was attempted, but the adverse reaction reappeared and the treatment was withdrawn.

A 55 year-old female hemodialysis patient with a hemoglobin of 10.7 g/dL, and a serum ferritin of 12 ng/ml was started on i.v. ferric gluconate. After the first and second doses, the patient experienced intense epigastric pain lasting 3-4 hours, and no further doses were administered.

A 50 year-old woman on hemodialysis was receiving 80U/kg i.v. of EPO, and had a hemoglobin of 9.7 g/dL and serum ferritin of 22 ng/ml. Immediately following a slow infusion of 125 mg of ferric gluconate, an anaphylactoid

reaction, characterized by severe hypotension, parasthesias of lips, fingers, and genitalia, without respiratory arrest, occurred. This reaction resolved after 1 hour.

Allegra V et. al., "Iron Deficiency in Maintenance Hemodialysis Patients: Assessment of Diagnosis Criteria and of Three Different Iron Treatments," Nephron 1991 57 175

In this study, the effect of 2 oral and 1 intravenous iron preparations, on hemoglobin, hematocrit, iron studies and red blood cell indices, were compared in maintenance hemodialysis patients.

A total of 72 maintenance hemodialysis patients of mean age 51 years, on hemodialysis for a mean of 57 months, were studied. Patients underwent hemodialysis three times a week. Patients with chronic inflammatory diseases, hepatitis, bleeding, or patients taking androgens, were excluded from the study. No patients had received a blood transfusion for the previous 3 months.

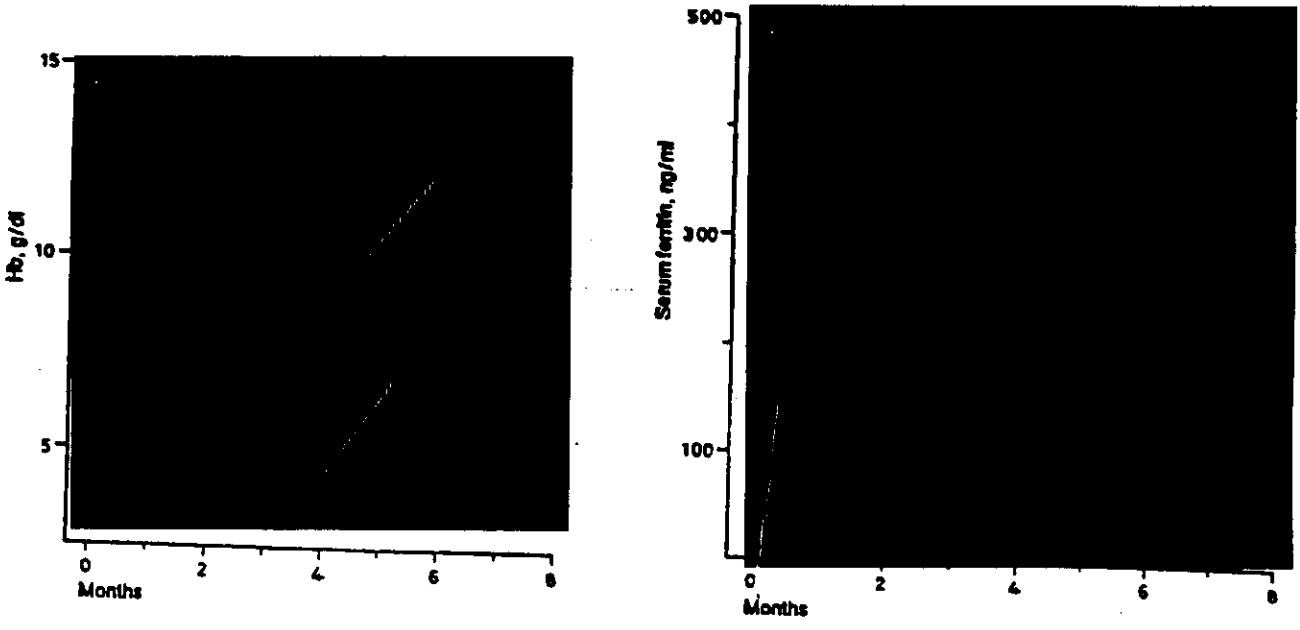
Patients were divided into 3 groups, based on their baseline serum ferritin values: **Group A**; > 191 ng/ml, **Group B**; 19 to 191 ng/ml, and **Group C**; < 19 ng/ml. Each of these groups was further divided into **3 treatment subgroups**: 1) oral Fe-ferritin; 67.5 mg/day of Fe+3, 2) oral Fe-chondroitin sulfate; 60 mg/day of Fe+3, or 3) i.v. Fe-Gluconate Sodium; 31 mg of Fe+3 at the end of each dialysis session. Patients received iron for a total of 6 months. Follow-up was continued for 6 months after ending iron therapy.

The rate of "positive" hemoglobin responses at 6 months are shown in the table below. Note that a "positive" response was defined as an increase of ≥ 15% of the baseline value.

	Group A	Group B	Group C
Treatment 1	0/5(0%)	2/10(20%)	1/7(14%)
Treatment 2	0/5(0%)	1/6(17%)	3/7(43%)
Treatment 3	0/7(0%)	5/11(45%)	10/16(63%)

Note that for all iron preparations (Treatments 1 - 3), greater increases in hemoglobin were seen for patients with lower baseline serum ferritin values. The greatest increases were seen for i.v. Ferric Gluconate, compared to the two oral iron preparations. Hemoglobin and serum ferritin responses for patients who received i.v. Ferric Gluconate, AND had baseline

serum ferritin values of < 191 ng/ml (i.e. Groups B and C of Treatment 3 patients) are shown below. Note that study medication was stopped after 6 months.



No adverse events were reported with the use of i.v. Ferric Gluconate in this study.

Summary of Published Reports

A summary of the published reports of the use of Ferrlecit to treat iron deficiency in chronic hemodialysis patients is shown below (Table 16, vol. 21, pp. 45-6).

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Summary Table of Published Reports of the use of Ferrlecit in Chronic Hemodialysis Patients

Study	Patients treated with Fe-gluconate	Dose of Fe-gluconate	Hemoglobin (g/dL) Response	Serum Ferritin (SF; µg/L) Response
Navarro, et al.	27	375mg (62.5mg/month for 6 months)	Maintained at starting level (±1) Baseline Mean: 10.7 6 month Mean: 10.6	Stable throughout study Baseline Mean: 187 6 month Mean: 196
Taylor, et al.	46	125mg/wk, 62.5 mg/wk, or 62.5 mg/fortnight for 6 months[1]	Pts w/ normal SF at Baseline BL: 9.05 6 mo: 11.25 Pts w/ low SF at Baseline BL: 10.05 6 mo: 11.00	Pts w/ normal SF at Baseline BL: 176 6 mo: 304.5 Pts w/ low SF at Baseline BL: 68 6 mo: 210.5
Pascual, et al.	40	1000mg (125mg @ 8 dialysis sessions)	I[2] BL: 8.7 6 mo: 9.9 II BL: 8.7 6 mo: 10.2 III BL: 9.4 6 mo: 9.8	I BL: 27 6 mo: 108 II BL: 29 6 mo: 113 III BL: 27 6 mo: 149
Pascual, et al.	19	1000mg (125mg @ 8 dialysis sessions)	I BL: 7.7 6 mo: 8.6 II BL: 8.4 6 mo: 9.6 III BL: 8.5 6 mo: 10.3	I BL: 23 6 mo: 111 II BL: 28 6 mo: 197 III BL: 26 6 mo: 154
Allegro, et al.	34[3]	31mg/dialytic session for 6 mo	15/34[4] responded (≥1g% increase from BL, including 5 who had not responded to oral iron; all had BL SF < 191mg/L)	Initial rapid and significant increase, followed by slow decrease after end of therapy
	11	20mg/dialytic session for 6 mo	11/11 responded, all were iron deficient at baseline	Gradual increase until Hemoglobin stabilized, then rapid increase

[1] Pts = Patients
[2] Dosage was based on serum ferritin level and was adjusted throughout the treatment period.
[3] BL = Baseline; mo = Month
[4] These 34 pts were compared with 40 pts receiving oral iron supplements.
[5] This rate of response was significantly higher than corresponding rate in pts receiving oral iron.

Note that, in addition to the favorable hemoglobin and serum ferritin responses, Ferrlecit was reported to decrease both the EPO dose, and maintenance intravenous iron requirements in the study by Taylor et. al.

Of the 177 renal dialysis patients exposed to Ferrlecit in the above studies, 3 experienced serious adverse events (Nephrol Dial Tranplant 1992 7 271): 1) malaise, heat, vomiting, and loin pain, which recurred on drug rechallenge and prohibited further drug use; 2) intense epigastric pain lasting 3-4 hours, which recurred on drug rechallenge, and prohibited further drug use, and; 3) an anaphylactoid reaction.

Integrated Summary of Safety

Those studies which were included in the Integrated Summary of Safety are tabulated below (Table 1, vol. 22, pp. 3-4).

Studies Included in the ISS

Study Title and Design	Starting Date/Status	No. Enrolled	Treatment No. Treated	Dose	Age Range (Mean)	% M/F	% W/B/O	Duration of Drug Treatment
Controlled Pivotal Study								
5600-01 Open-label, comparative, parallel, randomized, safety and efficacy study of Ferrlecit® at 2 dose levels in patients with end-stage renal disease on long-term hemodialysis	06/02/95 Complete	113	Ferrlecit: 41 Ferrlecit: 47 Control: 25	62.5 mg/dial. sess. 125 mg/dial. sess.	22-83 (55) 20-87 (57.1) 25-84 (52.2)	18/23 21/25* 8/17	30/8/3 36/5/6 10/8/7	8 doses 8 doses
Supportive Controlled Study								
5600-03 Open-label, computerate-use, comparative, safety and efficacy study of Ferrlecit® in patients with end-stage renal disease on long-term hemodialysis	05/28/94 Complete	63	Ferrlecit: 38 Control: 25	Variable (62.5 to 1000 mg)	22-84 (55.5) 25-84 (52.2)	24/14 8/17	36/0/2 10/8/7	Variable
Published Supportive Studies								
Allegra, Mangoni, Vanlia, 1991 *Iron deficiency in maintenance hemodialysis patients: Assessment of diagnostic criteria and of 3 different iron treatments.*	Complete	63	Fe-gluconate-Na: 34 Fe-gluconate-Na: 11	31 mg/dial. sess. 20 mg/dial. sess.	18-70 (51)	X/X*	X/X/X	6 months
Taylor, Peat, Porter, Morgan, 1996 *Regular low-dose intravenous iron therapy improves response to Erythropoietin in hemodialysis patients.*	Complete	46	Sodium ferric gluconate complex: 46	62.5 mg 2 x weekly 62.5 mg weekly 62.5 mg Q 2 weeks	34-82 (67)	31/15	X/X/X	6 months
Navarro, Teruel, Llabo, Morales, Ortuño, 1996 *Effectiveness of intravenous administration of Fe-Gluconate-Na complex to maintain adequate body iron stores in hemodialysis patients.*	Complete	58	Sodium ferric gluconate complex: 27	62.5 mg/month	28-79 (57)	14/13	X/X/X	6 months
Zanen, Adriaanse, van Bezeenel, Postkuma, de Jong, 1996 *'Overestimation' of transferrin after intravenous ferric gluconate (Ferrlecit®) in hemodialysis patients.*	Complete	20§ 2§	Ferrlecit: 17 Ferrlecit: 19 Ferrlecit: 2	62.5 mg/dial. sess. 125 mg/dial. sess. 125 mg/dial. sess.	34-75 (X) 34-82 (X) XX-XX (X)	11/6 11/8 X/X	X/X/X X/X/X X/X/X	1 dose X
Pascual, Teruel, Llabo, Basnds, Ortuño, 1992 *Serious adverse reactions after intravenous ferric gluconate.*	Complete	63	Ferrlecit: 63	125 mg/dial. sess.	XX-XX (X)	X/X	X/X/X	8 doses
Other Sources								
Nimmons and Lindsay *Maintenance studies.*	Ongoing	33	Ferrlecit: 33	125 mg/dial. sess. 62.5 mg maintenance	XX-XX (X)	X/X	X/X/X	X
Polak and Strobos *Manuscript in press*	Complete	NA	Ferrlecit: NA	NA	NA	NA	NA	NA
TOTAL PATIENTS IN CLINICAL STUDIES:		Ferrlecit: 473¶ Control: 25¶	Ferrlecit: 343¶ Control: 25¶					

Several patients were in more than 1 group. Twenty different patients were treated in this study.
§ These 2 patients were treated before the study began and, therefore, are not counted in the total number enrolled. They are counted in the number treated.
¶ The historical control group used in the 5600-01 study was the same group used in the 5600-03 study, so they are counted only once in the total.

* Gender was not reported for 1 patient in this group.
+ X = data not reported.

Published Supportive Studies included in the ISS

In addition to the published reports submitted to support the efficacy of Ferrlecit (discussed previously), another article was cited to further address the safety of Ferrlecit in hemodialysis patients, and is discussed below.

Zamen AL, et. al., "Oversaturation of transferrin after intravenous ferric gluconate (Ferrlecit®) in hemodialysis patients," Nephrol Dial Transplant 1996 11 820

Following the development of nausea, facial reddening, and hypotension in 2 chronic hemodialysis patients who were receiving monthly infusions of 62.5 to 125 mg of Ferrlecit, the authors determined that these patients had a TSAT >100% at the time of symptoms, and postulated that these symptoms may have been the result of acute iron toxicity. Thus, the present study of the use of intravenous ferric gluconate in iron-deficient hemodialysis patients, with particular attention serum iron studies, was conducted.

Participating patients were on maintenance hemodialysis 3 times a week, for 4 hours per session. All patients had either a transferrin saturation under 20%, or a serum ferritin less than 100 ng/ml. Most patients were receiving EPO. Ferric Gluconate was administered in one of four ways: **Protocol A** - 125 mg infusion over 30 minutes at the end of dialysis, **Protocol B** - 62.5 mg infusion over 30 minutes at the end of dialysis, **Protocol C** - 125 mg infusion over 4 hours during dialysis, and **Protocol D** - 62.5 mg infusion over 4 hours during dialysis.

Patient characteristics are shown below:

Protocol	A	B	C	D
N	10	7	9	10
Mean age (yrs)	67	71	64	62
Sex (M:F)	5:5	4:3	6:3	7:3
Mean Weight (kg)	66	69	65	67
No. Pts. On EPO	8	7	8	9

All 7 patients in the Protocol B group were also included in Protocol A. Three patients in the Protocol C group were also in Protocol A, and two of these were also in Protocol B. Protocol D shared five patients with Protocol C.

Infusion of ferric gluconate resulted in an immediate rise in serum iron and transferrin saturation, which reached a maximum at the end of administration, and dropping rapidly at the end of the infusion. The serum iron level after a given dose varied among patients. Peak serum iron and transferrin saturation levels are shown below:

Protocol	A	B	C	D
Serum Iron (µmol/l) Median Range	120 40-159	61 50-96	83 43-106	39 31-55
Iron Saturation (%) Median Range	207 84-331	118 91-174	141 88-172	78 43-92

Rises in serum iron and transferrin saturation were higher following a 30 minute, compared to a 4 hour infusion.

No adverse events were reported in this study.

Hematocrit, total protein, albumin, transferrin, ferritin, and LDH did not change during the iron infusion. Ferritin levels increased in all patients at the start of the next dialysis session, two days later.

The authors concluded that:

The commonly used rapid infusion rate (Protocol A) of Ferric Gluconate causes 'oversaturation' of transferrin. This is compatible with iron toxicity due to free iron which may explain our patients; complaints. Infusion during a longer period at a lower dose (Protocol D) is effective and eliminates 'oversaturation' of transferrin and probably the danger of iron toxicity.

Maintenance Studies Included in the ISS (from Lindsay and Nissenson)

Lindsay Study

As per vol. 22, pg. 45:

Beginning in July, 1996, Dr. Robert Lindsay at London Health Services, Ontario, Canada, had administered Ferrlecit Injection to dialysis patients on a compassionate-use and maintenance basis. The following protocol was adopted: 1) test dose administration of 25 mg in 50 mL of normal saline over one hour; 2) therapeutic administration of 125 mg in 100 ml of normal

saline over one hour for eight consecutive dialysis sessions; and 3) maintenance administration of 62.5 mg in 50 mL of normal saline over 30 minutes, once weekly following iron repletion.

Twenty-nine patients were treated between 7/28/96 thorough 11/22/97. Data entry captured the first 10 dosage administrations, i.e. through the first maintenance dose. Eleven patients completed the first 10 doses according to the protocol. Seven patients were switched to maintenance dosing early. Six patients ended the protocol before completion of 10 doses, or the protocol was not complete by 11/22/97. Patient specific modifications were made on 5 patients. There were a total of 278 separate drug administrations in these 29 patients.

No patient discontinued study drug due to an adverse event. No patient experienced a serious adverse event. There were 13 adverse events that the clinical coordinator felt were possibly or probably related to drug therapy, or where the relationship was unknown. These adverse events occurred in 11/29 (or 38%) patients, and are summarized below (vol. 22, pp. 47-9).

Adverse Events that Occurred in the Compassionate-Use, Maintenance Study of Lindsay et. al.

Patient	Adverse Event	Total Dose
100 64 M	Flushing	1087.5 mg
101 62 M	Transient tachycardia Nausea and vomiting	962.5 mg
107 56 M	Nausea Itching	1087.5 mg
108 48 F	Flushing	1087.5 mg
109 64 M	Headache	900 mg
112 85 M	Transient hypotension	837.5 mg
113 27 M	Abdominal pain Malaise	1150 mg
116 69 M	Transient hypotension Nausea and vomiting	1087.5 mg
118 73 F	Flush	1087.5 mg
127 64 F	Sweating	1025 mg
128 70 M	Flatulence	775 mg

Nissenson Study

Dr. Allen Nissenson treated 4 patients with a documented anaphylactic reaction to iron dextran, with Ferrlecit. One of these was patient #141 of study 5600-01, and was treated without incident. The characteristics and outcomes of the remaining four patients are shown below (vol. 22, p. 50). No adverse events were observed in these patients.

Adverse Events in Patients with a Previous Anaphylactic Reaction to Iron Dextran

	Patient Number			
Variable	102	101	104	105
Dextran Reaction	Anaphylaxis	Anaphylaxis	SOB, chest pain, hypotension	Anaphylaxis
Age	84	24	53	66
Gender	Male	Male	Female	Male
Etiology CRF	Diabetes	Glomerulonephritis	Alport's Syndrome	Diabetes
Total Ferrlecit	900 mg	1000 mg	900 mg	1000 mg
Administrations	8	9	8	9
Dates	10/3/96-12/12/96	9/16/96-11/20/96	10/21/96-12/24/96	10/21/96-12/24/96
AE	None	None	None	None

Serious Adverse Events - European Data

Ferrlecit Injection has been used since 1959 in over 20 countries outside the United States. Countries with recent (1990-1995) sales or marketing shipments include: Germany, Italy, Spain, Saudi Arabia, Austria, the Netherlands, Belgium, Luxembourg, Poland, the Czech Republic, Slovakia, Hungary, Israel, Lithuania, Estonia, Russian Federation, Byelorussia, Ukraine, Croatia, Uzbekistan, Myanmar, Dubai, South Africa, and Uruguay. The majority of current usage is in Germany, Italy, and Spain. The principal intravenous usage is among the 48,000 hemodialysis patients in Germany.

There have been no withdrawals of marketing approval for Ferrlecit in any country. Formal registration in the Netherlands lapsed in 1986, as sales in this country did not justify the fee for re-registration.

Note that iron dextrans are sold primarily in the United States and United Kingdom, and have been available for over 30 years. They are not used in Germany, and not available in Italy.

Adverse events collected by Rhone-Polenc Rorer, the manufacturer of Ferrlecit, for both the oral and intravenous preparations, are summarized below (vol. 23, pp. 46-68). Note that approximately 90% of the use of Ferrlecit in Italy is oral, while most all the use of Ferrlecit in Germany is the intravenous formulation for hemodialysis patients.

Adverse events reported in Italy from 1995-96 are tabulated below. All adverse events were classified as "serious", and all outcomes were listed as "recovery."

Adverse Events Reported in Italy
1995-96

Patient	Adverse Event
40 F	Anaphylactoid reaction
36 F	Allergic reaction
43 F	Allergic reaction, back pain
60 M	Allergic reaction, back pain
27 F	Allergic reaction
50 F	Anaphylactoid reaction
45 F	Anaphylactoid reaction
26 F	Allergic reaction, laryngismus, uterine spasm
46 F	Anaphylactoid reaction
70 M	Heart arrest, apnea
64 M	Convulsion, apnea
19 F	Apnea, vasodilation, abdominal pain
52 F	Tremor, fever
50 F	Dyspnea, back pain, headache

Adverse events reported in Germany from 1992-96 are tabulated below. All adverse events were classified as "serious," and all outcomes were listed as "recovery," unless otherwise specified.

Adverse Events Reported in Germany
1992-96

Patient	Adverse Event
42 F	Anaphylactoid reaction (Outcome "unknown")
30 F	Anaphylactoid reaction
Unk F	Allergic reaction, hemolysis (Outcome "ongoing")
19 F	Allergic reaction
67 F	Allergic reaction, back pain, abdominal pain, increased cough
25 F	Anaphylactoid reaction
22 F	Allergic reaction, dyspnea
30 F	Anaphylactoid reaction
32 F	Allergic reaction (Outcome was "significant disability")
30 F	Allergic reaction, chest pain, dizziness, dyspnea, hypertension
57 F	Shock
40 F	Allergic reaction, vasodilation, anxiety, paraesthesia
23 F	Anaphylactoid reaction, rash
Unk F	Anapylactoid reaction, heart arrest
48 F	Shock, headache
24 F	Shock, dyspnea, somnolence
Unk F	Shock, convulsion (Outcome "unknown")
Unk F	Convulsion
76 M	Shock, dyspnea, respiratory disorder
85 F	Apnea
83 F	Heart arrest
41 F	Lung edema (Outcome "unknown")
47 M	Chest pain
47 F	Chest pain
53 F	Chest pain
71 M	Hypertension
58 M	Vesiculobullous rash
45 F	Vesiculobullous rash
79 M	Vesiculobullous rash
35 F	Peripheral edema
50 F	Breast carcinoma (Outcome was "significant disability")

Allergic and Anaphylactic Adverse Events - European Data

As seen above, the primary adverse events associated with the use of Ferrlecit Injection were allergic/anaphylactoid. The comparative nature and incidence of these events were summarized in a report by Gerald Faich MD MPH, and Jur Strobos MD JD entitled, "Ferrlecit injection: safer intravenous iron therapy than iron dextrans." Dr. Faich is the former Director of the Office of Epidemiology and Biostatistics, Center for Drugs, FDA. This study was funded by R&D Laboratories, [redacted]. Information from this report is presented below (vol. 23, pp. 2ff.).

Methodology

To determine use patterns and provide denominators for rate calculations, data on the use of (Ferrlecit and Iron Dextran) were obtained from marketing sources and manufacturers. Adverse event reports and listings were obtained from the World Health Organization Collaborating Center for Drug Monitoring, Rhone-Poulenc Rorer GmBH (the manufacturer of Ferrlecit), Schein Pharmaceutical Inc. (a manufacturer of an iron dextran), and the German Health Ministry.

Total Drug Exposure

Ferrlecit Injection

Ferrlecit Injection was first introduced for intravenous use in 1959. A summary table of the number of Ferrlecit units (of 2 or 5 mls per unit) is shown below:

Number of Ferrlecit Units Sold
(by Country and Year)

	1992	1993	1994	1995	1996
[redacted]					

[redacted]

German usage was primarily in hemodialysis patients. Of the 30,000-45,000 hemodialysis patients in Germany, 60%-75% require maintenance intravenous iron supplementation, of approximately one ampule/patient/week. This accounts for [redacted] ampules per year, or over [redacted] of the total yearly Ferrlecit Injection usage in Germany. Parenteral drug exposure in Italy provides an additional [redacted] doses of Ferrlecit per year, for a total of 2.7 million exposures per year. Drug exposure in Spain was excluded from this study, due to poor adverse event reporting practices.

Iron Dextran

Approximately [redacted] doses of Iron Dextran were sold in 1995; 90% for use in renal hemodialysis patients.

Cumulative Allergic and Anaphylactic Adverse Events

Ferrlecit Injection

All Ferrlecit-related allergic adverse events that were reported in Italy and Germany from 1976-1996 are tabulated below (Table 1, vol. 23, p. 16). These data were collected from manufacturer electronic databases, reports provided by the German Health Ministry, case report forms compiled by the manufacturer's quality assurance program in Germany, and the World Health Organization Collaborating Center for Drug Monitoring (Uppsala, Sweden) database. "Allergic reactions" were defined as those that manifested as rash or flushing, without edema or hypotension. "Anaphylactoid reactions" were defined as those that included hypotension, collapse, edema, cardiac arrest, or dyspnea.

Allergic and Anaphylactoid Reports for Ferrlecit from 1976-1996 for Italy and Germany Combined

Year	Allergic	Anaphylactoid	Total
1976	-	1	1
1977	-	-	-
1978	-	2	2*
1979	-	2	2
1980	-	2	2*
1981	-	2	2
1982	-	2	2
1983	-	3	3
1984	-	1	1
1985	-	-	-
1986	1	10	11**
1987	1	-	1
1988	-	1	1
1989	-	1	1
1990	-	-	-
1991	-	-	-
1992	1	1	2
1993	1	3	4
1994	1	7	8
1995	-	25	25***
1996	-	6	6
Total	5	69	74

* Multiple reports from a clinical site with identical symptoms were excluded. As a result, 17 patients with "flush and dyspnea" from one practice, and 10 reports of "shock-like condition" from one clinic were excluded. No deaths were reported at either site.

** Several group reports from a single practice.

*** See subsequent discussion of "batch production problems with Ferrlecit".

An additional breakdown of the above adverse events by country, and by whether death or diability resulted, is shown below (Table 2, vol. 23, p. 17).

Allergic and Anaphylactoid Reports for Ferrlecit from 1976-1996

	Italy	Germany
Cases in 1992	0	2
in 1993	0	4
in 1994	2	6
in 1995	9	16
in 1996	3	3
Total cases	14	31
Total 3rd/4th Qtr. 1995	7	11
Known Surviving	14	28
Deaths	0	0
Disabilities	0	1
Mean age	44.6	42.4

Based on the above 1992-96 data of 45 reports over 5 years, at an estimated use rate of [redacted] ampules sold (or 5 years [redacted] doses sold per year), the reporting rate of allergic/anaphylactoid reactions for Ferrlecit Injection was 3.3 per million doses.

Batch Production Problems with Ferrlecit

The large increase in anaphylactoid reactions in 1995 (i.e. 8 in 1994, and 25 in 1995) prompted an investigation of batch production records by the manufacturer. High molecular weight polysaccharides, probably α-1,6-glucans, in a new commercial source of sucrose, was identified as the culprit. When production was switched to the original source of sucrose, reports of allergic/anaphylactoid adverse events dropped (from 25 in 1995, to 6 in 1996).

Iron Dextran

Several literature reviews have addressed the risks of serious or life-threatening adverse events with the use of iron dextran. Hamstra et. al.(JAMA 1980 243 1726), retrospectively examined the experience of 481 patients who received a total of 2099 intravenous doses of 250 or 500 mg of iron dextran. There were 3(0.6%) life-threatening, and 12(2.6%) non-life-threatening, systemic, allergic reactions. Thus, 23% of reported allergic reactions were life-threatening.

Woodman et. al.(Pharm Med 1987 1 289), reported an anaphylactoid adverse event rate of 1.8% among 1260 patients given iron dextran.

Fishbane et. al.(Am J Kidney Dis 1996 28 529), retrospectively identified 573 hemodialysis patients who were given iron dextran, and identified 10(1.7%) anaphylactoid, and 4(0.7%) serious reactions. Thus, 29% of reported allergic reactions were serious.

Faich et. al. (unpublished data), examined the hospital records from a 100-hospital network database (maintained by [redacted]). There were 549,705 hospital discharges during a six-month period in 1996. Of these, 5979 patients had a diagnosis of renal hemodialysis, and 474 of these had received iron dextran during their hospital stay. Five of these 474 patients also received epinephrine during the same hospital stay, resulting in a calculated rate of anaphylaxis of 1.1%.

There were 196 World Health Organization reports of allergy or anaphylactoid reactions in the United States from 1976-1996. These are summarized in the table below (Table 3, vol. 23, p. 18).

Allergic and Anaphylactic Adverse Event Reports for Iron Dextran Received by WHO from 1976-1996

Year	Number	Deaths	Known survival or recovery
1976	3	2	1
77	3	1	1
78	1		1
79	4		3
80	4		1
81	2		1
82	7	1	4
83	8	1	3
84	8		5
85	5	1	3
86	10	2	2
87	3	1	0
88	5	2	0
89	13	1	0
90	16	2	1
91	14	2	0
92	6		0
93	16	2	2
94	26	2	5
95	26	7	1
96	16	4	2
Total	196	31	36

Fatality Rates

During the period 1976-96, there were 74 reports of allergic or anaphylactoid reactions for Ferrlecit Injection from Italy and Germany, and 196 reports for iron dextran from the United States. No deaths were reported in Ferrlecit-treated patients, and 3 had unknown outcomes. There were 31(16%) deaths in patients who received iron dextran, while the outcome was unknown for 129(66%) cases.

Note that important limitations of analyses which attempt to compare the incidences of allergic/anaphylactoid reactions in patients treated with iron dextran or ferric gluconate, include significant underreporting and differences in the reporting patterns of different countries.

SUMMARY AND CONCLUSIONS

Two sponsor-conducted studies were submitted to support the approval of Ferrlecit as "**first line treatment for iron deficiency anemia in renal hemodialysis patients on supplemental recombinant human erythropoietin**": studies 5600-01 and 5600-03.

Study 5600-01 was a 3-center, randomized, open-label, historically-controlled, comparative study of a high- and low-dose i.v. Ferrlecit regimen, in 108 iron-deficient chronic hemodialysis patients. Study 5600-03 was a single-center, non-randomized, open-label, variable-dose, compassionate-use, historically-controlled study of the use of i.v. Ferrlecit in 63 iron-deficient chronic hemodialysis patients. Additional studies, including 252 Ferrlecit-treated patients from the published literature, and postmarketing information from Europe, were also submitted to support the safety and efficacy of Ferrlecit in chronic renal dialysis patients.

Summary of Study 5600-01

Study 5600-01 was a 3-center, randomized, open-label, historically-controlled, study of the safety and efficacy of 500 mg (low-dose) and 1000 mg (high-dose) of Ferrlecit® in iron-deficient hemodialysis patients. Study medication was given in 8 divided doses, during 8 sequential dialysis sessions (or a period of 16 to 17 days). The primary endpoint was the change in hemoglobin from baseline to the last available observation through Day 40.

Eligibility for this study (including protocol amendments) included chronic hemodialysis patients with a hemoglobin below 10 g/dL (or hematocrit at or below 32%), and serum ferritin below 100 ng/mL or iron saturation below 18%. Exclusion criteria included significant underlying disease or inflammatory conditions, or an EPO requirement of greater than 10,000 units t.i.w. Parenteral iron and red cell transfusions were not allowed for 2 months prior to, and during the study. Oral iron was not allowed for Ferrlecit-treated patients.

The historical control population consisted of 25 chronic hemodialysis patients associated with the University of Colorado Health Sciences Center. Due to drug unavailability, intravenous iron dextran was discontinued in these patients for 14 months. All patients were to have stable EPO doses and hematocrit values for at least 2 months prior to iron dextran discontinuation, however "many of the patients received blood transfusions before

the beginning of the study". All patients received oral iron supplementation throughout the study, although dose and patient compliance were not monitored. Safety data was not collected.

The intent-to-treat population consisted of 39 patients in the low-dose Ferrlecit group, 44 patients in the high-dose Ferrlecit group, and 25 historical control patients. Three patients in the low-dose group were enrolled but did not meet the inclusion criteria (hemoglobin or ferritin levels were too high).

A total of 5 patients were withdrawn from the study. Two discontinued for logistic reasons. One patient was withdrawn after development of pruritis and chest pain following the test dose. One patient in the high-dose group was withdrawn following the development of nausea, abdominal pain, flank pain, fatigue, and rash following the first treatment dose. One patient in the low-dose group was withdrawn after the development of a "red, blotchy rash" following the first treatment.

Ten EPO dosage changes occurred during the course of study drug administration: 4 patients had increases, and 2 patients had decreases in their EPO doses in the low-dose group; and 3 patients had increases, and 1 patient had a decrease in their EPO doses in the high-dose group.

Fourteen EPO dosage changes occurred after the administration of study drug: 6 patients had increases, and 2 patients had decreases in their EPO doses in the low-dose group; and 2 patients had increases, and 4 patients had decreases in their EPO doses in the high-dose group.

Thus, the per-protocol population consisted of 24 low-dose Ferrlecit patients, 35 high-dose Ferrlecit patients, and 25 historical control patients. These numbers represent 59%, 78%, and 100%, of the intent-to-treat low-dose, high-dose, and historical control populations, respectively.

Patient populations were similar with respect to baseline demographics, hemoglobin, hematocrit, iron studies, and red blood cell indices, with the exception that there were more white Ferrlecit-treated patients, and the serum ferritin was significantly higher in historical control patients (605.6 ng/mL in historical control patients, compared to 105.6 ng/mL in low-dose and 88.4 ng/mL in high-dose patients).

The mean baseline hemoglobin and hematocrit were similar between treatment and historical control patients, and were 9.6 g/dL, and 29%, respectively.

Mean changes in hemoglobin from baseline were small (0.3 g/dL in the low-dose, and 1.1 g/dL in the high-dose intent-to-treat patients; and 0.5 g/dL in the low-dose, and 1.2 g/dL in the high-dose per-protocol patients).

Mean changes in hemoglobin from baseline, for both the intent-to-treat and per-protocol populations, increased within each dose group, and were greater in the high-dose compared to the low-dose Ferrlecit groups.

When compared to the historical control, mean changes in hemoglobin from baseline, for both the intent-to-treat and per-protocol populations, were higher for the high-dose compared to either low-dose or historical control patients. Mean changes in hemoglobin from baseline were similar in the low-dose and historical control patients.

The observed increases in hemoglobin were supported by the results for the hematocrit and iron studies, for both the intent-to-treat and per-protocol patients. Specifically, serum iron, percent iron saturation, and serum ferritin increased by 11.7 µg/dL, 8.5%, and 199.4 ng/mL, respectively, in high-dose intent-to-treat patients; and 10.8 µg/dL, 8.3%, and 175.1 ng/mL, respectively, in high-dose per-protocol patients.

No treatment-by-investigator interactions were reported, and no significant associations of age, race, or gender were found for the observed increases in hemoglobin from baseline.

ANCOVA analyses designed to determine the effects of confounding variables on the primary efficacy outcome, found that the baseline hemoglobin, and dose of Ferrlecit (high-dose > low-dose); and NOT changes in EPO dose, had significant effects on the observed increases in hemoglobin. Because a significant effect of baseline EPO dose on the change in hemoglobin was noted in the analysis which included results from historical control patients, an ANCOVA analysis which included the covariates of treatment effect, baseline hemoglobin, baseline EPO dose, and change in EPO dose, was performed. This analysis reconfirmed the significantly greater increases of hemoglobin and hematocrit in high-dose, compared to low-dose or historical control patients.

The primary Ferrlecit-associated adverse events were allergic reactions that occurred in 3 patients, and resulted in premature study discontinuation. Available information for these cases is shown below:

Patient	Reasons for Study Discontinuation
116	Patient withdrew after the development of pruritis and chest pain following the test dose of Ferrlecit.
311	Patient was in the high-dose group, and experienced nausea, abdominal and flank pain, fatigue, and rash following the first dose of Ferrlecit.
335	Patient was in the low-dose group, and experienced a "red, blotchy rash" following the first dose of Ferrlecit.

The incidence of patients who experienced an allergic reaction in this study was 3/83 Ferrlecit-treated patients, or 3.6%. No anaphylactoid reactions, i.e. those including hypotension, edema, dyspnea, or cardiac arrest, were reported.

Summary of Study 5600-03

Study 5600-03 was a single-center, non-randomized, open-label, historically-controlled, variable-dose, compassionate-use study of the safety and efficacy of Ferrlecit in iron-deficient hemodialysis patients. The primary efficacy variable was the change in hemoglobin from baseline to the last available observation through Day 50.

Inclusion and exclusion criteria were identical to those of Study 5600-01, as was the historical control population. Sixty-three patients were evaluated in this study: 38 in the Ferrlecit-treated group, and 25 patients in the historical control group.

Ferrlecit-treated patients were considered to have completed the study per protocol, if they received at least 8 doses of study medication. A total of 14(37%) of completed the study per protocol. Twelve (32%) Ferrlecit-treated patients received less than 8 doses, and 12(32%) patients had incomplete dosing information. Not all patients received Ferrlecit at consecutive dialysis sessions, and many Ferrlecit-treated patients received oral iron during the study (no further information was provided).

Overall the Ferrlecit-treated group was comprised of more: males, males of age ≤ 65 years, and Caucasians. The mean weight of Ferrlecit-treated patients was 180 kg, compared to a mean weight of 144 kg in historical control patients.

Baseline hemoglobin and hematocrit values were similar between the treatment and control groups, and were 9.1 g/dL and 27.3%, respectively, for Ferrlecit-treated patients. Serum iron studies were also similar between treatment and control groups, with the exception of serum ferritin, which was 606 ng/mL for

historical control patients, compared to 77 ng/mL for Ferrlecit-treated patients.

Mean increases in hemoglobin from baseline were small, and similar to those seen observed in study 5600-01; 0.4 g/dL in historical control patients, and 1.3 g/dL in Ferrlecit-treated patients. Within-in group changes in hemoglobin were statistically significant for Ferrlecit-treated, and not historical control patients.

Non-statistically-significant increases in serum iron, percent iron saturation, and serum transferrin were noted in Ferrlecit-treated patients.

No significant effect of age or race on changes in hemoglobin or hematocrit were reported. A significant treatment-by-gender interaction was noted for female patients however: females in the Ferrlicit-treated group had significantly greater increases in hemoglobin and hematocrit, than females in the historical control group). Changes in hemoglobin were not significantly affected by baseline EPO doses.

Of the 38 patients exposed to Ferrlecit in this study, 1 patient experienced an adverse event(s) that resulted in premature study discontinuation, required hospitalization, and was felt by the on-site investigator to be "probably" related to study drug. Specifically, patient #552 discontinued due to "dizziness, lightheadedness, diplopia, malaise, and weakness", after receiving a total of 125 mg of Ferrlecit.

In summary, interpretation of the results of Study 5600-03 is limited by the fact that this study was a small, single-center, compassionate-use, variable-dose, historically-controlled trial. However, the results of study 5600-03 corroborate the results of study 5600-01, and thus support the efficacy of Ferrlecit for iron replacement therapy in chronic hemodialysis patients.

Summary of the Literature Studies Submitted to Support the Efficacy of Ferrlecit in Renal Dialysis Patients

A summary of the published reports of the use of Ferrlecit to treat iron deficiency in chronic hemodialysis patients is shown below.

Summary Table of Published Reports of the Use of Ferrlecit in Chronic Hemodialysis Patients

Study	Patients treated with Fe-gluconate	Dose of Fe-gluconate	Hemoglobin (g/dL) Response	Serum Ferritin (SF; µg/L) Response
Navarro, et al.	27	375mg (62.5mg/month for 6 months)	Maintained at starting level (±1) Baseline Mean: 10.7 6 month Mean: 10.6	Stable throughout study Baseline Mean: 187 6 month Mean: 196
Taylor, et al.	46	125mg/wk, 62.5 mg/wk, or 62.5 mg/fortnight for 6 months[2]	Pts w/ normal SF at Baseline BL: 9.85 6 mo: 11.25 Pts w/ low SF at Baseline BL: 10.05 6 mo: 11.00	Pts w/ normal SF at Baseline BL: 176 6 mo: 304.5 Pts w/ low SF at Baseline BL: 68 6 mo: 210.5
Pascual, et al.	40	1000mg (125mg @ 8 dialysis sessions)	I[3] BL: 8.7 6 mo: 9.9 II BL: 8.7 6 mo: 10.2 III BL: 9.4 6 mo: 9.8	I BL: 27 6 mo: 108 II BL: 29 6 mo: 113 III BL: 27 6 mo: 149
Pascual, et al.	19	1000mg (125mg @ 8 dialysis sessions)	I BL: 7.7 6 mo: 8.6 II BL: 8.4 6 mo: 9.6 III BL: 8.5 6 mo: 10.3	I BL: 23 6 mo: 111 II BL: 28 6 mo: 197 III BL: 26 6 mo: 154
Allegro, et al.	34[4]	31mg/dialytic session for 6 mo	15/34[5] responded (≥15% increase from BL, including 5 who had not responded to oral iron; all had BL SF ≤ 191mg/L)	Initial rapid and significant increase, followed by slow decrease after end of therapy
	11	20mg/dialytic session for 6 mo	11/11 responded, all were iron deficient at baseline	Gradual increase until Hemoglobin stabilized, then rapid increase

1. Pts = Patients
2. Dosage was based on serum ferritin level and was adjusted throughout the treatment period.
3. BL = Baseline; mo = Month
4. These 34 pts were compared with 40 pts receiving oral iron supplements.
5. This rate of response was significantly higher than corresponding rate in pts receiving oral iron.

Overall, the efficacy of Ferrlecit as iron-replacement therapy in chronic renal dialysis patients, is supported by the above published reports, which employed various dosing regimens of Ferrlecit, and which adequately represent the available literature (as determined from an independent MEDLINE search). Relevant efficacy outcomes in these studies included hemoglobin and serum ferritin responses, as well as a reduction of EPO dosage and maintenance intravenous iron requirements.

With respect to safety, of the 177 renal dialysis patients exposed to Ferrlecit in the above published studies, 3(1.7%) patients experienced serious adverse events: 1) malaise, heat, vomiting, and loin pain, which recurred on drug rechallenge and prohibited further drug use; 2) intense epigastric pain lasting

3-4 hours, which recurred on drug rechallenge, and prohibited further drug use, and; 3) an anaphylactoid reaction. The overall safety experience with Ferrlecit is subsequently discussed.

Overall Safety Experience with Ferrlecit

The Integrated Summary of Safety for this NDA included safety information from: Studies 5600-01 and -03, published reports, two small "maintanence" studies, and post-marketing data from Italy and Germany.

The primary Ferrlecit-associated adverse events in Study 5600-01, were allergic reactions that occurred in 3 out of a total of 83 (or 3.6% of) Ferrlecit-treated patients, and which resulted in premature study discontinuation. Available information for these cases is summarized below:

Patient	Reasons for Study Discontinuation
116	Patient withdrew after the development of pruritis and chest pain following the test dose of Ferrlecit.
311	Patient was in the high-dose group, and experienced nausea, abdominal and flank pain, fatigue, and rash following the first dose of Ferrlecit.
335	Patient was in the low-dose group, and experienced a "red, blotchy rash" following the first dose of Ferrlecit.

Of the 38 patients exposed to Ferrlecit in Study 5600-03, 1 patient (or 2.6%) experienced an adverse event(s) that resulted in premature study discontinuation, required hospitalization, and was felt by the on-site investigator to be "probably" related to study drug. Specifically, patient #552 discontinued due to "dizziness, lightheadedness, diplopia, malaise, and weakness", after receiving a total of 125 mg of Ferrlecit.

Of the 177 renal dialysis patients exposed to Ferrlecit in the previously-discussed published literature, 3(1.7%) patients experienced serious adverse events, which were: 1) malaise, heat, vomiting, and loin pain, which recurred on drug rechallenge and prohibited further drug use; 2) intense epigastric pain lasting 3-4 hours, which recurred on drug rechallenge, and prohibited further drug use, and; 3) an anaphylactoid reaction.

An additional published report by Zamen et. al., entitled, "Oversaturation of transferrin after intravenous ferric gluconate (Ferrlecit®) in hemodialysis patients," (Nephrol Dial Transplant 1996 11 820), conducted a study of peak serum iron study values following the i.v. administration of Ferrlecit. This study was initiated following development of nausea, facial reddening, and

hypotension in 2 chronic hemodialysis patients who were receiving monthly infusions of 62.5 to 125 mg of Ferrlecit, and who were also determined to have TSAT values of > 100% at the time of symptoms. The authors found that longer infusions and lower doses of Ferrlecit resulted in lower peak serum iron, and iron saturation values. The relationship of serum iron study values and the development of nausea, facial reddening, and flushing however, was not established in this study.

Two "maintenance studies" were submitted to provide further information of the use of Ferrlecit in chronic hemodialysis patients. The first was a compassionate-use, single-center study of 29 chronic hemodialysis patients who were administered 125 mg of i.v. Ferrlecit for 8 consecutive dialysis sessions, followed by a maintenance dose of 62.5 mg once weekly. No patient in this study discontinued study drug due to an adverse event, and there were no serious adverse events. A total of 13 adverse events occurred in 11 patients that the clinical coordinator felt were possibly or probably related to drug therapy. These reactions included flushing (3 patients), nausea and/or vomiting (3 patients), and transient hypotension, abdominal pain, sweating, headache, and flatulence (1 patient each).

The second "maintenance study" was a trial conducted by Dr. Allen Nissenson, who treated a total of 5 chronic hemodialysis patients with a history of anaphylaxis to iron dextran, with up to 1000 mg of i.v. Ferrlecit. No adverse events resulted.

Ferrlecit Injection has been used since 1959 in over 20 countries outside of the United States. Ninety-seven percent of the total sales of Ferrlecit in 1996 were in Germany, Italy, and Spain; over 80% of it's use in Germany is in renal hemodialysis patients, while 90% of it's use in Italy is as an oral dietary supplement.

Postmarketing information from Germany and Italy was obtained from the manufacturer of Ferrlecit (Rhone Polenc Rorer). Most all reported serious adverse events were allergic/anaphylactoid in nature. During the period 1976-96, there were 74 reports of allergic/anaphylactoid reactions for Ferrlecit Injection from Italy and Germany; none resulted in death, although 3 had unknown outcomes.

Notably, an increase in the number of reported anaphylactiod reactions in 1995 (i.e. 8 in 1994, and 25 in 1995) prompted an investigation of batch production records by the manufacturer. High molecular weight polysaccharides, probably α-1,6-glucans, in a new commercial source of sucrose, was identified as the culprit. When production was switched to the original source of

sucrose, reports of allergic/anaphylactoid adverse events dropped (from 25 in 1995 to 6 in 1996).

In a sponsor-supported study by Faich and Strobos entitled, "Ferrlecit injection: safer intravenous iron therapy than iron dextrans," information was provided which indicated that the use of Ferrlecit results in a decreased reporting rate of allergic/anaphylactoid reactions, and decreased case fatality rate. However, significant underreporting, and differences in the reporting patterns of different countries, complicate the interpretation of these results.

OVERALL CONCLUSIONS

The efficacy of Ferrlecit for the treatment of anemia in iron-deficient renal hemodialysis patients was primarily supported by the results of the dose-comparison concurrent control study 5600-01. Additional supportive information included the compassionate-use study 5600-03, as well as several reports from the literature.

Eligibility criteria for Study 5600-01 included a hemoglobin of < 10 g/dL or hematocrit of < 32%; and a serum ferritin of < 100 ng/mL or iron saturation of < 18%, in chronic renal dialysis patients who were receiving erythropoietin. Pre- and post-therapy results for intent-to-treat patients who received the high-dose Ferrlecit regimen (i.e. 1000 mg divided over 8 consecutive dialysis sessions) are summarized below.

Mean Pre- and Post-Therapy Results for High-Dose Ferrlecit Patients in Study 5600-01 (Intent-to-Treat Population)

	PRE-THERAPY	POST-THERAPY
Hemoglobin (g/dL)	9.6	10.7
Hematocrit (%)	29	33
Iron saturation (%)	16	25
Serum Ferritin (ng/mL)	88	287

Note that the above post-therapy results approach the target values that are recommended by the National Kidney Foundation (Amer J Kid Dis 1997 30 S194); viz., a hemoglobin of 11-12 g/dL, hematocrit of 33-36%, iron saturation ≥20% (and <50%), and serum ferritin ≥100 ng/mL (and <800 ng/mL).

Note also that the results of patients who received the low-dose Ferrlecit regimen (i.e. 500 mg divided over 8 dialysis sessions), were equivalent to those of historical control patients, who received oral iron therapy only.

The primary safety concern with the use of Ferrlecit is the incidence of allergic/anaphylactoid reactions. These reactions occurred at a rate of 3.6% in Study 5600-01, 2.6% in Study 5600-03, 1.7% in the available published literature, and there have been 74 reports to the manufacturer of allergic/anaphylactoid reactions in the past 20 years from Italy and Germany. There have been no known deaths associated with these adverse events. It is notable that Ferrlecit was safely used in 5 hemodialysis patients with a history of anaphylaxis to iron dextran.

In conclusion, it is recommended that Ferrlecit be approved for "the treatment of iron deficiency anemia in chronic renal hemodialysis patients on supplemental erythropoietin therapy". The recommended dose should be the high-dose regimen used in Study 5600-01, viz., 125 mg of Ferrlecit in 100 ml of normal saline, given intravenously over 60 minutes, for 8 consecutive dialysis sessions. The risk of allergic/anaphylactoid reactions should be adequately (and prominently) addressed in the professional labeling.

Follow-up studies to determine the optimal dosing regimens for repeat courses of Ferrlecit (should a repeat course be necessary for iron repletion); and for maintenance therapy (once iron repletion has been achieved) are recommended. Further information on the use of Ferrlecit in hemodialysis patients with a history of anaphylaxis to iron dextran should also be collected. In addition, whether the concomitant use of angiotensin converting enzyme inhibitors increases the risk of allergic/anaphylactoid adverse events, as reported by Rolla G et. al. (J Allergy Clin Immunol 1994 93 1074), should be determined.

/S/ [redacted] 5/7/98
Kurt Sizer, M.D.

cc:
NDA 20-995
HFD-180
HFD-180/LTalarico
HFD-180/KSizer
HFD-181/CSO
HFD-180/JChoudary
HFD-180/EDuffy
f/t 5/7/98 jgw
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/S/ [redacted] 5-4-98