CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020955

STATISTICAL REVIEW(S)

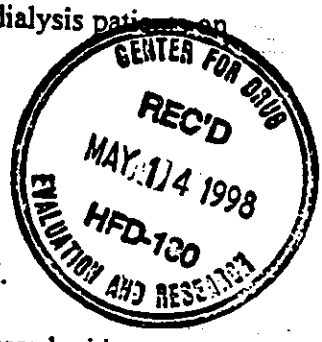
STATISTICAL REVIEW AND EVALUATION

NDA: 20-955 Date: MAY 13 1998

APPLICANT: R&D Laboratories.

NAME OF DRUG: Ferrlecit (sodium ferric gluconate complex in sucrose) Injection.

INDICATION: First line treatment for iron deficiency anemia in renal hemodialysis pati[illegible] on supplemental recombinant human erythropoietin (epoietin).



USER FEE DUE DATE: June 30, 1998.

DRUG CLASSIFICATION: 1P.

DOCUMENT REVIEWED: NDA Volumes 4 to 14 dated December 30, 1997.

MEDICAL REVIEWER: The issues addressed in this review have been discussed with medical reviewer, Kurt Sizer, MD., HFD-180

STATISTICAL REVIEWER: Wen-Jen Chen, Ph.D.

1.0 . INTRODUCTION

The role of erythropoietin in the management of anemia associated with chronic renal failure (CRF) is now well established. It is estimated that more than half of renal hemodialysis patients are presently treated with recombinant human erythropoietin (rHuEPO). However, some of these patients may not receive the full benefit of rHuEPO therapy for a variety of reasons. A common cause of failure to respond to rHuEPO is lack of adequate iron stores and availability of iron for erythropoiesis. Although gastrointestinal absorption of iron is essentially normal in End Stage Renal Disease (ESRD) patients, somewhat less than 10% of a given oral dose of iron is utilized even under the best of conditions. In many cases, therefore, oral iron supplementation is not sufficient to replete iron stores and the intravenous administration for iron is required.

Intravenous iron is a frequent route of administration in patients with low ferritin levels and low transferrin saturations. For theses patients, administration at the time of hemodialysis offers a unique opportunity to provide the necessary iron through an intravenous line. Ferrlecit is a product for the administration of iron intravenously in patients with iron deficiency anemia in whom oral use is unsatisfactory or impossible.

This submission consists of two studies, Study# 5600-01 and Study# 5600-03, in support of the safety and efficacy of Ferrlecit in the first line treatment for iron deficiency anemia in renal hemodialysis patients on supplemental recombinant human erythropoietin. As indicated by the sponsor, in this application, Study# 5600-01 was considered pivotal and Study# 5600-03 was considered supportive of Study# 5600-01.

2.0 STUDY# 5600-01

2.1 Background Information

Objectives: The objective of this study was to evaluate the safety and efficacy of Ferrlecit, an iron supplement administered intravenously, in patients with end-stage renal disease (ESRD) and iron deficiency anemia who were on long-term hemodialysis.

Study Design: This study was designed as an open-label, multi-center, double-dose (Ferrlecit), historical-control, and randomized clinical trial. The prospective study was conducted in two centers in the United States and one center in Canada between August 2, 1995 and March 23, 1996.

Two doses of Ferrlecit, low-dose (500 mg) group and high-dose (1000 mg) group, were compared to a historical control group. The historical control group came from a single center and consisted of ESRD patients who were on iron medication. For the assessment of drug effects, Ferrlecit treatments at the two dose levels were compared with each other and with the historical control.

Patients were assigned to the two dose groups (low-dose and high-dose groups) by randomization while the historical-control group of patients was recruited from the chronic hemodialysis patients from the University of Colorado Health Sciences Center. In addition, the sponsor emphasized that blinding was unnecessary in this study because the relevant, clinically significant endpoints were limited to laboratory assessments that could not be influenced by knowledge of treatment category.

Study Population: The inclusion criteria for the study population included ferritin levels below 200 ng/ml or iron saturation below 18%, hemoglobin below 10 gm/dl or hematocrit below 30%, and patients on chronic hemodialysis. The exclusion criteria included patients with unstable chronic disease, HIV positive, or hepatitis B surface antigen positive patients, erythropoetin resistance, and patients receiving parenteral iron and/or investigational drugs with the potential to interfere with iron metabolism within two months of study initiation (for details, refer to the inclusion and exclusion criteria described in sponsor's section 6.3, Volume 1.16).

Treatments Administered: The treatment administration for the patients in each of the two dose-groups is described below:

1. Patients from each of the two dose-control groups were administered a test dose of 25 mg Ferrlecit on Study Day -5 (5 days prior to initiation of treatment).
2. Patients in the low-dose group were administered a total of 500 mg of Ferrlecit in 8 divided doses of 62.5 mg each. The doses were administered in 50 mL normal saline over 30 minutes toward the end of hemodialysis at sequential hemodialysis sessions that were uniformly scheduled 3 times per week. Consequently, the duration of the treatment period for each patient was approximately 16 or 17 days, following a test-dose of 25 mg administered at Day -5.
3. Patients in the high-dose group were administered a total of 1000 mg of Ferrlecit in 8 divided doses of 125 mg each. The doses were administered in 100 mL normal saline over 60 minutes toward the end of hemodialysis at sequential hemodialysis sessions that were uniformly scheduled 3 times per week. Consequently, the duration of the treatment period for each patient was approximately 16 or 17 days, following a test dose of 25 mg administered at Day -5.

Prior and Concomitant Therapy: Parental iron products, including blood transfusions, or other investigational drugs were not allowed during the 2 months preceding study initiation or during the study. Erythropoietin therapy was limited to ≤ 10,000 units 3 times per week.

Laboratory Assessment Schedule: The regular laboratory assessment schedule for the dose-control and historical-control groups was: Day 19, 31, and 47 for dose-control groups and Day 30 and 60 for historical-control group.

Primary and Secondary Efficacy Variables: The primary efficacy variable was the change in hemoglobin from baseline to the endpoint time (last available observation through Day 40: Day 31 for Ferrlecit groups and Day 30 for historical-control group). The 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 corpuslar hemoglobin concentration (MCHC) [no primary or secondary efficacy variables were specified in the protocol].

Primary Analysis: The primary analysis was based on an intent-to-treat data set of 108 (83 Ferrlecit and 25 historical control) patients and used an analysis of variance/covariance (ANOVA/ANCOVA) statistical method (missing data replaced by the previous observation). The same statistical method was used to analyze a per-protocol defined data set, which excluded 29 patients for protocol violations.

Secondary Analysis: The secondary analysis used repeated measurement analysis ANOVA to analyze changes in baseline of the response outcomes at each of the regularly scheduled laboratory assessments (missing data replaced by the previous observation).

Disposition of Patients: Patient disposition is displayed in Table 2.1.1 (extracted from sponsor's Table 2, Volume 1.16).

Table 2.1.1 (Sponsor's) Patient Disposition

Disposition*	Low dose group N = 41	High dose group N = 47	Historical control N = 25	Total N = 113*
Entered (Safety)	41 (100%)	47 (100%)	25 (100%)	113 (100%)
Discontinued After test dose During study	 0 (0%) 2 (5%)	 2 (4%) 1 (2%)	 NA+ NA+	 2 (2%) 3 (3%)
Intent-to-treat&	39 (95%)	44 (94%)	25 (100%)	108 (96%)
Per-protocol**	24 (59%)	35 (74%)	25 (100%)	84 (74%)

*: One patient was screened but withdrew for personal reasons prior to receiving test dose and is not included in this table.
+: NA = Not Applicable.
&: All patients with baseline and endpoint efficacy values.
**: 5 patients discontinued; 3 patients did not meet inclusion criteria; 22 patients whose rHuEPOs were changed during the study were not included.

One-hundred thirteen (113) patients were enrolled in the study; 5 discontinued from the study (3 because of adverse events). 108 patients completed the study (39 in the low-dose group, 44 in the high-dose group, and 25 in the historical-control group).

2.2 Sponsor's statistical analysis and results

Comparison of patient demographics

The demographic variables analyzed by the sponsor for the three treatment groups (low dose, high dose, and historical control groups) are age, gender, race, height, and weight. The results indicated that there were no significant differences between low-dose and high-dose Ferrlecit groups for the above five demographic variables. Overall, age, gender, and weight were not significantly different among the 3 groups, but race was ($p=0.001$). There was a significantly higher percentage of white patients in the low-dose group ($p=0.003$) and in the high dose group ($p < 0.001$) when compared with the historical group.

The sponsor indicated that in general, patients in the treatment groups were similar in demographic characteristics, although each of the two dose groups contained a higher percentage of white patients than the historical control group. The difference in racial distribution most likely reflects differences in demographics of the investigation sites.

Comparison of Baseline Characteristics

Table 2.2.1 summarizes baseline data for ESRD patients in the intent-to treat (ITT) population.

The baseline variables analyzed by the sponsor were systolic blood pressure (BP), diastolic BP, pulse, respirations, baseline hemoglobin, baseline hematocrit, baseline percent iron saturation, baseline serum ferritin, baseline serum iron, baseline MCH, baseline MCV, and baseline MCHC.

Table 2.2.1 (Sponsor's) Summary of patient baseline variables#

Variables	p-value* Low Dose vs. High Dose	p-value Low Dose vs. Control	p-value High Dose vs. Control	p-value Overall Test
Systolic BP	0.030	<0.001	0.032	0.001
Diastolic BP	0.077	0.031	0.337	0.057
Pulse	0.327	0.072	0.246	0.184
Respirations	0.98	NA+	NA	0.98
Baseline Hemoglobin	0.298	0.038	0.220	0.114
Baseline Hematocrit	0.305	0.212	0.705	0.401
Baseline Percent Iron Saturation	0.026	0.012	0.530	0.020
Baseline Serum Ferritin	0.678	<0.001	<0.001	<0.001
Baseline Serum Iron	0.112	0.007	0.162	0.024
Baseline MCH	0.691	0.055	0.022	0.060
Baseline MCV	0.705	0.001	<0.001	<0.001
Baseline MCHC	0.566	0.036	0.009	0.028

#: Extracted form sponsor's Table 3, Volume 1.16;
***: P-value is associated with an F test by using the ANOVA with effects for treatment groups;**
+: NA = Not Applicable.

The results from Table 2.2.1 indicate no significant differences between low-dose and high-dose Ferrlecit groups for the diastolic BP, pulse, respirations, baseline hemoglobin, baseline hematocrit, baseline serum ferritin, baseline serum iron, baseline MCH, baseline MCV, and baseline MCHC. However, systolic blood pressure was significantly lower in the low-dose group (p=0.03) and baseline percent iron saturation was significantly lower (p=0.026) in the high-dose group.

Overall, for baseline vital signs, a significant difference among the three treatment groups was observed in systolic blood pressure (p=0.001), while diastolic blood pressure, pulse rate, and respiration were similar. In addition, significant differences among the three treatment groups was observed for percent iron saturation, serum ferritin, serum iron, MCV, and MCHC (p=0.02, p<0.001, p=0.024, p<0.001, and p=0.028, respectively).

Comparing the low-dose group with the control group, baseline values for hemoglobin, percent iron saturation, serum iron, and MCHC were significantly higher in the low-dose group (p=0.038, p=0.012, p=0.007, p=0.036, respectively) than in the control group. Baseline values for

hematocrit and MCH were not significantly different between the two groups, but baseline values for serum ferritin and MCV were significantly higher ($p<0.001$ and $p=0.001$, respectively) in the control group than in the low-dose group.

Similarly, comparing the high-dose group with the control group, baseline values for hemoglobin, hematocrit, percent iron saturation, and serum iron were not significantly different between the 2 groups. However, baseline values for serum ferritin, MCH, and MCV were significantly higher ($p<0.001$, $p=0.022$, and $p<0.001$, respectively) in the control group than in the high-dose group. Finally, baseline value for MCHC was significantly lower ($p=0.009$) in the control group than in the high-dose group.

Summary of Sponsor's Efficacy Analysis Results

i) Primary analysis results

Table 2.2.2 and Table 2.2.3 summarize the primary analysis results for the primary and secondary efficacy variables, respectively. The outcome analyzed by ANCOVA is the change from baseline to the endpoint time (Day 31 for dose-control groups and Day 30 for historical-control group) for the ITT data set (change: endpoint - baseline).

In Table 2.2.3, only the secondary efficacy variables with p-values of ANCOVA for testing the mean differences between two treatment groups (high-dose vs. low-dose groups, low-dose vs. historical- control groups, or high-dose vs. historical-control groups) less than 0.05 are presented.

Table 2.2.2 (Sponsor's) Primary analysis of change in hemoglobin from baseline to the endpoint time using ITT patient data set#

Primary endpoint: Change in Hemoglobin	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
n (No.of patients in analysis)	39	44	24			
Mean	0.3	1.1	0.4	0.002	0.501	0.001
Within group paired t-test	p=0.072	P < 0.001	P=0.016			

#: Extracted from sponsor's Table 10, Volume 1.16.

***: P-value is associated with the ANOVA model (baseline efficacy variable used as a covariate).**

Table 2.2.3 (Sponsor's) Primary analysis of mean change in the secondary efficacy variables from baseline to the endpoint time using ITT patient data set#

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
Hematocrit (%)						
n (No.of patients in analysis)	39	44	24	0.002	0.140	<0.001
Mean	1.4	3.6	0.8			
Within group paired t-test	P= 0.018	P<0.001	P=0.112			
MCH (pg)						
n (No.of patients in analysis)	39	44	24	0.040	0.985	0.084
Mean	-0.1	0.6	-0.3			
Within group paired t-test	P= 0.712	P=0.007	P=0.385			
MCV (fl)						
n (No.of patients in analysis)	39	43	24	0.042	0.004	<0.001
Mean	0.7	2.3	-2.6			
Within group paired t-test	P= 0.102	P<0.001	P=0.011			
MCHC (g/dL)						
n (No.of patients in analysis)	39	44	24	0.222	0.019	0.169
Mean	-0.5	-0.2	0.6			
Within group paired t-test	P= 0.150	P=0.225	P<0.001			

#: Extracted from sponsor's Table 11, Volume 1.16.
*: P-value is associated with the ANCOVA (baseline efficacy variable used as a covariate).

The results in Table 2.2.2 indicate that a significant mean change in hemoglobin for the high-dose group compared to the low-dose group (p=0.002) or the historical control group (p=0.001). No significant difference in mean change in hemoglobin was found between the low-dose and historical-control groups. In addition, the results by the paired t-test showed a significant change from baseline in hemoglobin for the high-dose and historical control groups ($P < 0.001$ and p=0.016, respectively), but not for the low-dose group (p=0.072).

Table 2.2.3 indicates that mean changes in hematocrit, MCH, and MCV for the comparison in the high-dose group versus low-dose group (p=0.002, 0.04, and p=0.042, respectively) were in favor of high-dose. Furthermore, for hematocrit and MCV, the high-dose had significantly higher mean changes than the historical-control group (both p-values less than 0.001). Finally, the mean change in MCV was significantly greater in the low-dose group than that in the historical control group (p=0.004), but the mean change in MCHC was significantly greater in the historical control group than that in the low-dose group (p=0.019).

The results of the primary analysis using ITT data set for the two dose groups (high-dose versus low-dose groups) are provided in Appendix A.

For the per-protocol patients, the high-dose was significantly superior to the historical control regarding the mean change in hemoglobin, hematocrit, and MCV (p-values less than 0.001 for all three efficacy variables). However, in the comparisons of low-dose versus historical-control groups, the low-dose was shown superior to the historical control with respect to MCHC only (p=0.013).

ii) Secondary analysis results.

Table 2.2.4 (extracted from sponsor's Table 5, Volume 1.16) summarizes the secondary analysis of mean changes in primary and secondary endpoints from baseline to each of the regularly scheduled laboratory assessments (Day 19, 31, and 47).

Table 2.2.4 (Sponsor's) Repeated measures analysis of mean changes in primary and secondary endpoints from baseline to each scheduled assessment (Day 19, 31, and 47) using ITT patient data set

Efficacy Variable	P-Values*		
	TMT#	DAY	TMT*DAY
Hemoglobin (g/dL)	0.002	0.020	0.749
Hematocrit (%)	0.003	0.231	0.843
Percent Iron Saturation (%)	0.001	0.008	0.479
Serum Ferritin (ng/mL)	0.001	< 0.001	0.002
Serum Iron (ug/dL)	0.029	0.015	0.162
MCH (pg)	0.058	0.415	0.567
MCV (fl)	0.002	0.182	0.003
MCHC (g/dL)	0.642	0.003	0.240

*: P-values were from a mixed model with fixed effects for treatment, day, and treatment*day interaction and a random effect of patient nested within treatment.
#: TMT - Low-dose group vs. High-dose group.

Table 2.2.4 showed that under significance level of 0.05, the difference in mean hemoglobin change between the two dose groups remained stable overtime (TMT*DAY interaction not significant; p=0.749). The overall mean change in hemoglobin was significantly higher in the high-dose group than in the low-dose group (p=0.002).

Furthermore, the overall mean changes in hematocrit, percent iron saturation, and serum iron (all three variables without significant interactions between treatment and DAY) from baseline to each of the regularly scheduled laboratory assessments for the high-dose group were significantly greater than those for the low-dose group (p=0.003, p=0.001, and p=0.029, respectively).

For the per-protocol patients, sponsor's Table 8 (in Volume 1.16) indicated that the overall mean changes in hemoglobin, hematocrit, percent iron saturation, and MCH (all four variables without significant interactions between treatment and DAY) from baseline to each of the regularly scheduled laboratory assessments were significantly higher for the high-dose group than for the low-dose group ($p=0.018$, $p=0.030$, $p=0.030$, and $p=0.042$, respectively).

Results of safety

In dose-control comparisons, chest pain occurred more frequently in the high-dose group and leg edema occurred more frequently in the low-dose group. When compared to the historical control, however, both high dose and low dose patients experienced less chest pain. Leg edema was not reported for historical control patients. All other adverse events (AEs) were similar between the groups. The sponsor emphasized that no serious AEs or deaths were judged by the investigator to be related to study drug.

2.3 Reviewer's Analyses and Comments

In order to validate the sponsor's efficacy claim for this study, this reviewer performed two subgroup analyses, gender (male and female) and age group (senior: age > 65 and junior: age ≤ 65), and covariate analysis with baseline EPO and baseline efficacy variable as covariates on hemoglobin and hematocrit using ITT data set. Then, this reviewer will comment on the issue of missing data.

Reviewer's analysis results

The results for the subgroup analysis on gender are summarized in Table 2.3.1.1 (below).

Table 2.3.1.1 (Reviewer's) Analysis of mean changes in hemoglobin and hematocrit from baseline to the endpoint time using (ITT) patient data set[a]

Variable/Gender	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 (%)/Female n (No.of patients in analysis) Mean Within group paired t-test	21 0.371 P= 0.14	22 1.086 P<0.001	16 0.256 P=0.148	0.105	0.273	0.009
Hemoglobin (%)/Male n (No.of patients in analysis) Mean Within group paired t-test	18 0.272 P= 0.32	21 1.14 P<0.001	8 0.84 P=0.063	0.007	0.691	0.096
Hematocrit (%)/Female n (No.of patients in analysis) Mean Within group paired t-test	21 1.52 P= 0.062	22 3.73 P<0.001	16 0.313 P=0.4	0.085	0.07	<0.001
Hematocrit (%)/Male n (No.of patients in analysis) Mean Within group paired t-test	18 1.17 P= 0.164	21 3.52 P<0.001	8 1.78 P=0.197	0.01	0.94	0.054

[a]: Data provided by the sponsor (Jan. 23, 1998) in a floppy diskette.
*: P-value is associated with the ANCOVA.

Table 2.3.1.1 indicates that for the comparison between high-dose and low-dose, the mean change differences for both hemoglobin and hematocrit were higher for the high dose than the low dose in both sexes. But the overall significant results for high vs. low (Table 2.2.2 and 2.2.3) appear to be primarily due to effects in males.

A pictorial (histogram) display of the mean changes in hemoglobin and hematocrit from baseline to the endpoint time are given in Fig. 2.3.1.1 and Fig. 2.3.1.2, respectively.

Figure 2.3.1.1

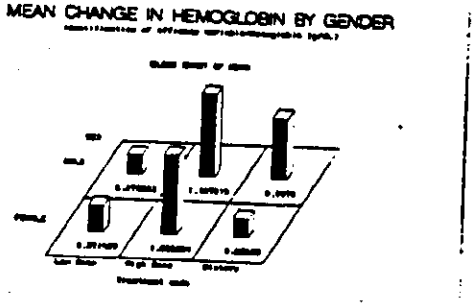
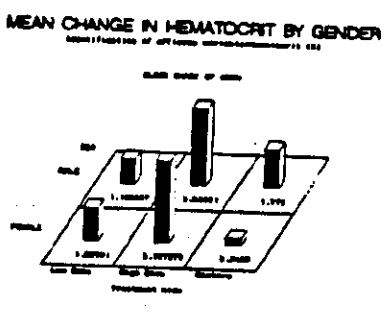


Figure 2.3.1.2



The results for the subgroup analysis on age group are summarized in Table 2.3.1.2.

Table 2.3.1.2 (Reviewer's) Analysis of mean changes in hemoglobin and hematocrit from baseline to the endpoint time using intent-to-treat patient data set[a]

Variable/Age Group	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 /65 Or Less n (No.of patients in analysis) Mean Within group paired t-test	28 0.207 P= 0.29	29 1.05 P<0.001	19 0.53 P=0.015	0.035	0.53	0.01
Hemoglobin /65+ Years n (No.of patients in analysis) Mean Within group paired t-test	11 0.627 P= 0.14	15 1.22 P<0.001	5 0.16 P=0.71	0.046	0.61	0.036
Hematocrit (%)/65 Or Less n (No.of patients in analysis) Mean Within group paired t-test	28 1.0 P= 0.11	29 3.45 P<0.001	19 1.08 P=0.072	0.054	0.21	0.002
Hematocrit (%)/65+ Years n (No.of patients in analysis) Mean Within group paired t-test	11 2.27 P= 0.087	15 3.93 P<0.001	5 -0.28 P=0.73	0.06	0.25	0.009

[a]: Data provided by the sponsor (Jan. 23, 1998) in a floppy diskette.
*: P-value is associated with the ANCOVA.

Table 2.3.1.2 indicates that for the comparison between high-dose and control groups, the mean change differences for both hemoglobin and hematocrit were significantly higher for the high dose group than the control group in both age groups.

The pictorial (histogram) display of the mean changes in hemoglobin and hematocrit from baseline to the endpoint time are given in Fig. 2.3.1.3 and Fig. 2.3.1.4, respectively.

Figure 2.3.1.3

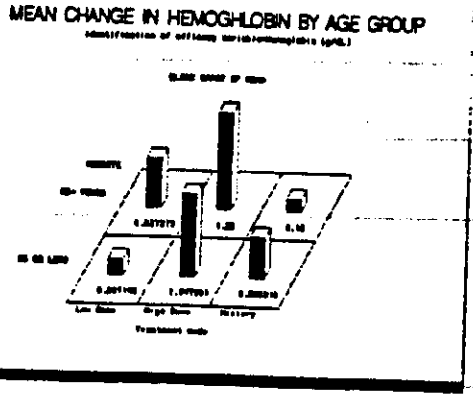
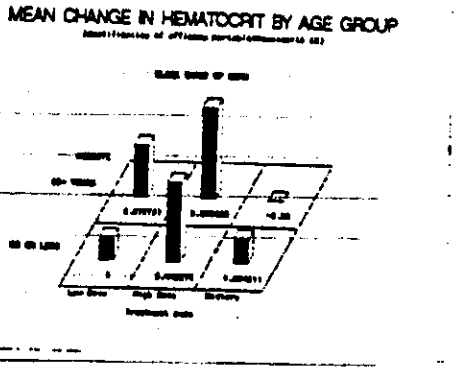


Figure 2.3.1.4



The results of this reviewer's covariance analysis using baseline efficacy variable and baseline EPO as covariates are summarized in Table 2.3.1.3 (below). Those results are also consistent with sponsor's primary analysis results.

Table 2.3.1.3 (Reviewer's) Primary analysis of mean change in hemoglobin and hematocrit from baseline to the endpoint time using ITT patient data set

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) Mean	39 0.3	44 1.1	24 0.4	0.0009	0.97	0.0065
Hematocrit (%) n (No.of patients in analysis) Mean	39 1.4	44 3.6	24 0.8	0.0012	0.46	0.0005

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

Comment on the issue of missing data

Since hemoglobin and hematocrit are considered as the most clinically relevant endpoints, Table 2.3.2.1 presents the number and percentage of missing values by treatment groups for the above two endpoints, calculated by using ITT data provided by the sponsor (March 19, 1998) in a floppy diskette.

Table 2.3.2.1 (Reviewer's) Missing values by visit day within each treatment group

Variable	Treatment Groups	Visit Day	Missing Number (%)
Hemoglobin	Low-Dose	19	0 (0%)
		31	0 (0%)
		47	1 (2.56%)
	High-Dose	19	0 (0%)
		31	0 (0%)
		47	1 (2.56%)
	History	30	1 (4%)
		60	2 (8%)
Hematocrit	Low-Dose	19	0 (0%)
		31	0 (0%)
		47	1 (2.56%)
	High-Dose	19	0 (0%)
		31	0 (0%)
		47	1 (2.56%)
	History	30	1 (4%)
		60	2 (8%)

From Table 2.3.2.1, we notice that the missing percentage for hemoglobin and hematocrit are less than 10%. Similar missing patterns are observed for the other parameters.

In order to assess the effect of the missing data and the robustness of the effect for Ferrlecit claimed by the sponsor, this reviewer applied generalized multivariate analysis of variance (GMANOVA) methodology on the intent-to-treat (ITT) data set. In this analysis, the missing values are not replaced. A GMANOVA model is formulated by baseline EPO, baseline efficacy variable, and three linear regression lines on visit-day for the three treatment groups (low-dose, high-dose, and historical-control groups). The results are presented in Table 2.3.2.2.

Table 2.3.2.2 (Reviewer's) Results of GMANOVA on mean changes from baseline to each of the regularly scheduled laboratory assessments using ITT patient data set

Variable	Treatment Group	Parameter Estimate (Intercept/Slope)	P-value for overall slope equality test	P-value for treatment equality test* H-vs.-L.	H.-vs.-C.	L.-vs.-C.
Hemoglobin	High-Dose	6.102/0.0095				
	Low-Dose	5.571/0.00762				
	Control	5.656/0.00011	0.39	0.0016	0.0007	0.433
Hematocrit	High-Dose	18.73/0.014				
	Low-Dose	17.02/0.013				
	Control	17.33/-0.016	0.32	0.0014	0.0002	0.29

***: Overall treatment effects (assessed in a common slope model) were significant for both hemoglobin and hematocrit under significance level of 0.05 (p=0.0004 and p=0.03, respectively).**

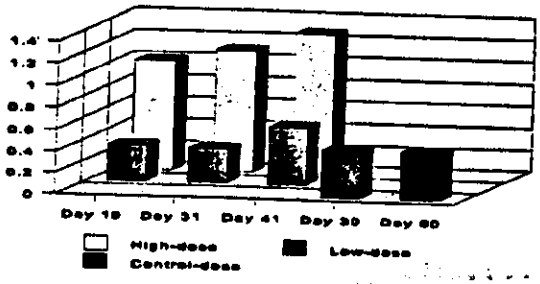
Table 2.3.2.2 indicates that the slopes on visit-day are not significantly different among the three treatment groups for both hemoglobin and hematocrit (P-value=0.39 and P-value=0.32, respectively). Therefore, the GMANOVA model (described above) with the common slope on visit day for the three treatment groups is used to assess the overall treatment effects among the three treatment groups for both hemoglobin and hematocrit.

The results indicate that the overall mean changes of the high-dose group in hemoglobin and hematocrit are significantly greater than those of the low-dose group and historical control group (p=0.0016 and p=0.0007 for hemoglobin high-dose vs. low-dose groups and high-dose vs. historical-control groups, respectively; p=0.0014 and p=0.0002 for hematocrit high-dose vs. low-dose groups and high-dose vs. historical-control groups, respectively). However, no significant differences between low-dose and historical-control groups are shown for both hemoglobin and hematocrit.

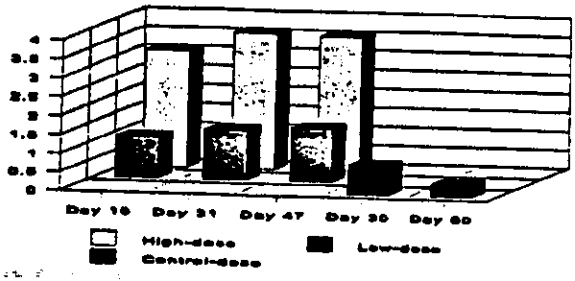
The pictorial (histogram) display of the mean changes in hemoglobin and hematocrit from baseline to the endpoint time are given in Fig. 2.3.2.1.

Fig. 2.3.2.1. Mean change from baseline to regularly scheduled laboratory assessments

Hemoglobin



Hematocrit



3.0 STUDY# 5600-03

3.1 Background Information

Objectives: The objective of this study was to evaluate the safety and efficacy of Ferrlecit, an iron supplement administered intravenously, in patients with end-stage renal disease (ESRD) and iron deficiency anemia who were on long-term hemodialysis.

Study Design: The study was designed as an open-label, compassionate-use, variable-dose, and historical-control study. The study was conducted in Canada.

Study Population: The Ferrlecit-treated group consisted of patients with ESRD on chronic hemodialysis. The historical control group consisted of patients with ESRD on chronic hemodialysis and supplemental rHuEPO, who were receiving orally administered iron (for detail, refer to the inclusion/exclusion criteria of Study# 5600-01 described in sponsor's section 6.3, Volume 1.16).

Treatments Administered: In the Ferrlecit-treatment group, Ferrlecit was administered in quantities of 62.5 mg or 125 mg per dialysis session; the patient's dose was the total cumulative amount of Ferrlecit received. In the historical control group, patients received orally administered iron supplementation.

Primary and Secondary Efficacy Variables: The primary efficacy variable was the change in hemoglobin from baseline to the endpoint time (last available observation through Day 50 for the Ferrlecit-treatment group and Day 60 for the historical control group). 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 corpuslar hemoglobin concentration (MCHC) indices.

Disposition of Patients: Patient disposition is displayed in Table 3.1.1 (extracted from sponsor's Table 2, Volume 1.20).

Table 3.1.1 (Sponsor's) Patient Disposition

Disposition	Ferrlecit N = 38	Control N = 25	Total N = 63
Entered	38 (100%)	25 (100%)	63 (100%)
Dosing data incomplete	12 (31.6%)	NA*	12 (19%)
< 8 doses of Ferrlecit	12 (31.6%)	NA	12 (19%)
Completed per protocol	14 (36.8%)	25 (100%)	39 (61.9%)

*: NA = Not Applicable.

Sixty-three (63) patients were entered in the study: 38 in the Ferrlecit-treatment group and 25 in the historical control group.

3.2 Sponsor's statistical analysis and results

Analysis of demographics

The demographic variables analyzed by the sponsor for the two treatment groups (Ferrlecit and control groups) were age, gender, race, height, and weight. The results indicated that the mean age was similar between the two groups ($p=0.429$), but gender, race, and mean weight were not evenly distributed between the two groups ($p=0.021$, $p<0.001$, and $p=0.012$, respectively) under significance level of 0.05.

Analysis of Baseline Characteristics

The baseline variables analyzed by the sponsor were systolic blood pressure (BP), diastolic BP, pulse, respiration, baseline hemoglobin, baseline hematocrit, baseline percent iron saturation, baseline serum ferritin, baseline serum iron, baseline MCH, baseline MCV, and baseline MCHC. The results showed that diastolic blood pressure and pulse ($p=0.601$ and $p=0.054$, respectively) were similar between the two groups. Systolic blood pressure was significantly lower ($p=0.001$) in the Ferrlecit treatment group than in the historical-control group.

In the comparison of efficacy variables at baseline between the two groups, hemoglobin, hematocrit, and serum iron values were similar between the two groups (p=0.243, p=0.05, and p=0.147, respectively). However, mean baseline percent iron saturation, serum ferritin, MCH, and MCV values were significantly higher in the control group than in the Ferrlecit-treated group (p=0.001 for percent iron saturation and p<0.001 for serum ferritin, MCH, and MCV). Finally, the mean baseline MCHC value was significantly higher in the Ferrlecit-treated group than in the control group (p=0.016).

Statistical methodology for efficacy analysis

The sponsor applied a paired t-test to analyze mean changes in efficacy variables (primary and secondary endpoints) from baseline to the endpoint time (last available observation through Day 50 for the Ferrlecit-treatment group and Day 60 for the control group) and analysis of covariance (ANCOVA) method to compare the differences of efficacy variables between the two treatment groups, using baseline efficacy variable as a covariate.

Results of the efficacy analysis

The efficacy results from ANCOVA indicated that mean changes in hemoglobin, hematocrit, and MCV from baseline to the endpoint time were significantly higher in the Ferrlecit-treated group than in the historical control group (p=0.022, p=0.002, and p<0.001, respectively). However, mean change in MCHC from baseline to the endpoint time was significantly higher in the historical control group than in the Ferrlecit-treated group (p=0.021). Mean changes in percent iron saturation, serum ferritin, serum iron, and MCH were not significantly different between the two groups. In addition, the results by the paired t-test showed that mean changes from baseline to the endpoint time in hemoglobin, hematocrit, percent iron saturation, serum ferritin, serum iron, MCHC, and MCV were significantly greater than zero for the Ferrlecit group (p<0.001 for hemoglobin, hematocrit, percent iron saturation, MCHC, and MCV; p=0.001 and 0.002 for serum ferritin and serum iron, respectively).

3.3 Reviewer's Analysis and Comment

Comment on the issue of missing data

Since hemoglobin and hematocrit are considered as the most clinically relevant endpoints, Table 3.3.1.1 presents the number and percentage of missing values by treatment groups for the above two endpoints, calculated by using ITT data set provided by the sponsor (March 19, 1998).

Table 3.3.1.1 (Reviewer's) Missing values by visit day within each treatment group

Variable	Treatment Groups	Visit Day	Missing Number (%)
Hemoglobin	Ferrlecit	20	0 (0%)
		50	0 (0%)
	History	30	1 (4%)
		60	2 (8%)
Hematocrit	Ferrlecit	20	0 (0%)
		50	0 (0%)
	History	30	1 (4%)
		60	2 (8%)

From Table 3.3.1.1, we noticed that the percent of missing information for either hemoglobin or hematocrit is less than 10%. Similar missing patterns were observed for the other parameters.

To assess the robustness of the observed treatment effect and the impact of missing data, this reviewer performed a repeated measures ANCOVA using ITT data set. In this analysis, missing values are not replaced. Data were analyzed at each of the following time periods: Day 20 and 50 for Ferrlecit group and Day 30 and 60 for historical control group. In the repeated measurement analysis, Day 30 and 60 were changed to Day 20 and 50, respectively. The model included treatment groups (Ferrlecit and historical control groups), baseline efficacy value, visit-day, and interaction between treatment and visit-day. The results are presented in Table 3.3.1.2.

Table 3.3.1.2 (Reviewer's) Repeated measures ANCOVA of mean changes from baseline to each of the two regularly scheduled laboratory assessments using ITT patient data set

Variables	p-Value Ferrlecit vs. Historical control
Hemoglobin	0.108
Hematocrit	0.023

Table 3.3.1.2 indicates that for hematocrit, the overall mean change of Ferrlecit group from baseline to the two regularly scheduled laboratory assessments (Day 20 and 50 for Ferrlecit group; Day 30 and 60 for historical control group) was significantly greater than that of the historical control group (p=0.023). For hemoglobin however, the p-value for the comparison of the overall mean change between Ferrlecit and historical control groups is 0.1084, indicating that the efficacy result is not robust.

4.0 CONCLUSION

The results of the efficacy analyses for Study# 5600-01 indicate that Ferrlecit high-dose (1000 mg) is effective in improving the levels of hemoglobin and hematocrit in ESRD patients on chronic hemodialysis when compared with low-dose and historical control on oral iron treatment. However, the Ferrlecit low-dose (500 mg) is not shown to be significantly different from the historical control group on the levels of hemoglobin and hematocrit in ESRD patients on chronic hemodialysis.

The results of the efficacy analysis from Study# 5600-03 provide support for the significant improvement of Ferrlecit on the levels of hemoglobin and hematocrit for the ESRD patients on chronic hemodialysis seen in Study# 56001-01.

APPEARS THIS WAY ON ORIGINAL

/S/

Wen-Jen Chen Ph.D.,
Mathematical Statistician

Concur: Dr. Sankoh /S/

Dr. Welch /S/ 1/13/98

cc: Archival NDA# 20-955
HFD-180 Div File
HFD-180/Dr. Talarico
HFD-180/Dr. Sizer
HFD-180/Mr. Strongin
HFD-720/Dr. Welch
HFD-720/Dr. Sankoh
HFD-720/Dr. Chen
HFD-720/File Copy
HFD-344 Dr. Barton.

APPEARS THIS WAY ON ORIGINAL

Appendix A

Table A.1 (Sponsor's) Primary analysis of change in hemoglobin from baseline to the endpoint time using ITT patient data set#

Change in Hemoglobin	Treatment 500 mg (N=39)	Treatment 1000 mg (N=44)	ANOVA P-value*
n (No.of patients in analysis)	39	44	0.001
Mean	0.3	1.1	
Within group paired t-test	p-value=0.072	p-value < 0.001	

Note: The interaction between treatment and investigator was not significant (p=0.136).
#: Extracted from sponsor's Table 4, Volume 1.16.
*: P-value is associated with an F test by using the ANOVA with effects of center and treatment.

Table A.2 (Sponsor's) Primary analysis of change in the secondary efficacy variables from baseline to the endpoint time using ITT patient data set#

Variable	Treatment 500 mg (N=39)	Treatment 1000 mg (N=44)	ANOVA P-value*
Hematocrit (%)			
n (No.of patients in analysis)	39	44	
Mean	1.4	3.6	
Within group paired t-test	P=0.018	P < 0.001	0.002
Percent Iron saturation (%)			
n (No.of patients in analysis)	38	43	
Mean	2.8	8.5	
Within group paired t-test	P = 0.156	P < 0.001	0.017
MCH (pg)			
n (No.of patients in analysis)	39	44	
Mean	-0.1	0.6	
Within group paired t-test	P = 0.712	P = 0.007	0.023
MCV (fl)			
n (No.of patients in analysis)	39	43	
Mean	0.7	2.3	
Within group paired t-test	P = 0.102	P < 0.001	0.013

#: Extracted from sponsor's Table 6, Volume 1.16 (variables with ANOVA p-value < 0.05 listed here).
*: P-value is associated with an F test by using the ANOVA with effects of center and treatment.