STATISTICAL REVIEW AND EVALUATION --- NDA
CLINICAL STUDIES

Medical Division: Gastrointestinal and Coagulant Drug Product (HFD-180)
Biometrics Division: Division of Biometrics II (HFD-715)

STATISTICAL KEY WORDS:
NDA #: 20-955
SERIAL NUMBER: 006
DATE RECEIVED BY CENTER: February 13, 2004
DRUG NAME: Ferrlecit (sodium ferric gluconate complex in sucrose) injection
INDICATION: Iron Deficiency Anemia
SPONSOR: Watson Pharma, Inc.
DOCUMENTS REVIEWED: Vol. 1, 23-37 Dated February 12, 2004
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A. Background

On August 9, 2002, FDA issued a Written Request for Pediatric Study, In accordance with this request the sponsor conducted a clinical study, entitled: A Randomized, Double-Blind, Parallel Group, Multicenter Study of the Efficacy of Two Doses of Ferrlecit in the Treatment of Iron Deficiency in Pediatric Hemodialysis Patients Receiving Epoetin (Study FR01006).

In the current NDA supplement, the sponsor seeks approval of Ferrlecit in the treatment of iron deficiency in pediatric patients from ≥ 6 years and < 16 years of age undergoing chronic hemodialysis (HD) and receiving supplemental erythropoietin therapy.

B. Study FR01006

1. Study Design

This was a randomized, double-blind, multiple dose, parallel-group, multicenter (26 sites), dose-response study of two dosage regimens of Ferrlecit (1.5 mg/kg or 3.0 mg/kg given eight times at sequential dialysis sessions) in pediatric HD patients (≥2 years and <16 years of age).

The primary objective of this study was to demonstrate and compare the effectiveness of two Ferrlecit doses in increasing hemoglobin in iron-deficient pediatric HD patients undergoing repletion Ferrlecit therapy.

Patients who had been determined to be iron deficient 4 weeks after discontinuation of all iron supplementation entered iron repletion therapy.

The study consisted of a 4 (or potentially 5) week Screening Period, an approximately 22 day repletion treatment period during which the patient was on a fixed and stable HD schedule (eight consecutive HD sessions over an approximate 22 day period), an evaluation of efficacy parameters 2 weeks after administration of the final Ferrlecit dose, and a final evaluation 4 weeks after administration of the final Ferrlecit dose.

At Screening Visit 1, potential participants were interviewed to establish their eligibility for inclusion in the study. Blood sample for measurement of Hgb, Hct, serum ferritin, and TSAT were collected. At Screening Visits 2, 3, and 4, blood samples for the measurement of Hgb were collected. At Screening Visit 5, blood samples for determination of baseline Hgb, Hct, serum ferritin, TSAT, reticulocyte hemoglobin content (CHr), and % hypochromic red blood cells (HCRBC) were collected. Patients meeting the criteria: TSAT <20%; and/or serum ferritin < 100 ng/mL, were eligible to enter the study.

Eligible patients were to be randomized to receiving Ferrlecit 1.5 mg/kg or Ferrlecit 3.0 mg/kg, infused intravenously by syringe pump over 1 hour, not to exceed 125 mg per dose, during each consecutive HD sessions for eight consecutive HD sessions over an approximate 22 day period.

Patients who were not iron deficient 4 weeks after discontinuation of all iron supplementation (i.e., at Screening Visit 5) were allowed to be re-screened 1 week later and enrolled in the study if, at that time, they met the criteria for iron deficiency. Patients who were still not iron deficient at the re-screening visit were to be discontinued from further study participation.

Baseline efficacy parameters were collected at the end of 4-week Screening Period (i.e., at Screening Visit 5). If the patient was enrolled in the study after re-screening, their baseline efficacy parameters were those collected at the re-screening visit.

Two weeks and 4 weeks after the last Ferrlecit administration, additional blood samples were obtained for determination of the patients Hgb, Hct, TSAT, serum ferritin, CHr, and HCRBC.

The primary efficacy parameter was the change in hemoglobin (Hgb) from baseline to 2 weeks after administration of the last Ferrlecit dose. Significant difference from zero in the change in Hgb from baseline to 2 weeks following the final Ferrlecit infusion was tested using paired t-tests for each Ferrlecit treatment separately for the completer population. A clinical significant change from baseline in Hgb was defined as 1.0 g/dL. Conclusions of significant changes from baseline were drawn when the changes were both statistically significant and clinically significant.

Secondary efficacy parameters were the change in Hct, TSAT, serum ferritin, CHr, and HCRBC from baseline to 2 weeks after the last study drug administration. Additionally, patients were classified as responders to treatment if they had an increase in Hgb of at least 1.0 g/dl.

The enrollment goal of the study was to enroll at least 29 male or female chronic HD pediatric patients with ESRD on stable erythropoietin (EPO) therapy at each dosing level (up to 58 patients, total).

The sample size estimation was made based on using a paired t-test to detect a significant difference from zero for the change from baseline in Hgb. Assuming a standard deviation of differences in Hgb of 1.6 g/dL, a minimum of 23 patients per dose group were needed to detect a significance difference for a change in Hgb from baseline of 1.0 g/dL with 80% power at α=0.05.

Due to the limit patient population for this disease, there was no sample size restrictions placed on this study. However, a sufficient number of patients needed to detect a significant difference in the primary efficacy parameter (approximately n=29 per dose group) were to be targeted for enrollment into the study.

2. Sponsor's Analysis

A total of 88 patients were screened for potential study participation. Of these 88 potential participants, 67 patents were enrolled and randomized (33 in 1.5 mg/kg Ferrlecit and 34 in 3.0 mg/kg Ferrlecit).

One patient (#2902) in the 1.5 mg/kg treatment group was withdrawn from the study because of kidney transplantation prior to receiving any study medication. As a result of this withdrawal, only 32 patients received study drug at the 1.5 mg/kg dose.

Of the 66 patients who received study drug, 59 patients (26 in 1.5 mg/kg group and 33 in 3.0 mg/kg group) completed the double-blind period and provided efficacy data at the HD session 2 weeks after their final Ferrlecit infusion.

Statistical analyses were performed using the following patient populations:

- Safety population: defined as all patients who were exposed to study medication.
- Completer population: defined as all patients who were exposed to study medication had no major protocol deviations, and provided data for the 2 weeks after the last Ferrecit administration visit.

Additionally, Observed Case (OC) dataset was defined for the purposes of analysis and summary:

- OC dataset: defined as those parameter values observed at each scheduled visit. Missing values were retained as missing.

Efficacy was evaluated in both the safety and completer populations. Nine patients (7 in 1.5 mg/kg group and 2 in 3.0 mg/kg group) were excluded from the completer population.

2.1 Treatment Group Comparability

The summary of results of comparability of treatment groups at baseline for safety population is given Appendix Table 1.

As seen from Appendix Table 1, no statistically significant differences between the two treatment groups were observed for demographic characteristics.

2.2 Sponsor's Analysis of Primary Efficacy Parameter

Repeated measurements of Hgb were taken during the 5 screening visits (SCV) prior to randomization. The results of these measurements showed a stable mean Hgb baseline of 9.4. g/dL during this time period.

The primary efficacy parameter was the change in hemoglobin (Hgb) from baseline to 2 weeks after administration of the last Ferrlecit dose. The mean changes from baseline in Hgb concentrations within each treatment group were tested using paired t-tests.

The results of change in hemoglobin (Hgb) from baseline to 2 weeks after administration of the last Ferrlecit dose for completer population are given below.

Hgb (g/dL) Response and its Change from Baseline (Completer Population)

	Baseline			2-Week			Change from Baseline			
Dose	n	Mean	(SD)	n	Mean	(SD)	n	Mean	(SD)	p-value
1.5 mg/kg	25	9.7	(2.1)	25	10.6	(2.2)	25	0.8	(1.30)	0.0033
3.0 mg/kg	32	9.4	(2.3)	32	10.4	(2.1)	32	0.9	(1.12)	<0.0001

Copied from Table 11.4-2
P-value was calculated using t-test.

As seen from table above, mean Hgb concentrations were statistically greater 2 weeks after the last Ferrlecit infusion compared to baseline values in both the 1.5 mg/kg and 3.0 mg/kg treatment groups. The Hgb change between the two treatment groups was not statistically different 2 weeks after the final Ferrlecit infusion (p=0.7547).

Clinical significance was defined as an increase from baseline in Hgb of ≥1.0 g/dL. The mean change from baseline in Hgb concentration was less than 1.0 g/dL for both treatment groups 2 weeks after the final Ferrlecit infusion and did not reach clinical significance.

2.3 Sponsor's Analysis of Secondary Efficacy Parameters

2.3.1 Responders to Therapy

A clinically significant change from baseline in Hgb was defined a priori as an increase in Hgb concentration of at least 1 g/dL two weeks after the last Ferrlecit infusion. A responder to therapy was defined as one who had both a statistically and a clinically significant change in Hgb two weeks after the last Ferrlecit infusion compared to baseline Hgb values.

The summary of results of responders to treatment 2 weeks after final Ferrlecit infusion is given below.

Summary of Responder to Treatment
(Completer Population)

Dose	Responder	95% Conf. Interval
1.5 mg/kg Ferrlecit	10/25 (40%)	(20.8%, 59.2%)
3.0 mg/kg Ferrlecit	16/32 (50%)	(32.7%, 67.3%)

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As seen from table above, , there was no statistical difference in the number of responders to treatment between the two treatment groups (p=0.4519).

2.3.2 Hct, TSAT, Serum Ferritin, CHr, and HCRBC Assessments

The results of change in Hct (%), TSAT (%), serum ferritin (ng/ml), CHr (pg), and HCRBC (5) from baseline to 2 weeks after administration of the last Ferrlecit dose for completer population are given below.

Change in Secondary Efficacy Variables from Baseline to
(Completer Population)

Hct (%)

	Baseline			2-Week			Change from Baseline			
Dose	n	Mean	(SD)	n	Mean	(SD)	N	Mean	(SD)	p-value
1.5 mg/kg	25	29.3	(6.9)	25	31.9	(6.6)	25	2.6	(3.9)	0.0031
3.0 mg/kg	32	28.4	(6.8)	32	31.4	(6.5)	32	3.0	(3.7)	<0.0001

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TSAT (%)

	Baseline			2-Week			Change from Baseline			
Dose	n	Mean	(SD)	n	Mean	(SD)	N	Mean	(SD)	p-value
1.5 mg/kg	24	19.8	(10.3)	25	24.9	(12.9)	25	5.5	(11.0)	0.0096
3.0 mg/kg	32	16.2	(10.6)	32	26.7	(16.4)	32	10.5	(14.0)	<0.0001

Copied from Table 11.4-4
P-value was calculated using signed rank test.

Serum Ferritin (ng/ml)

Dose	Baseline n	Mean	(SD)	2-Week n	Mean	(SD)	Change from Baseline N	Mean	(SD)	p-value
1.5 mg/kg	25	87.8	(120.1)	25	279.6	(327.2)	25	191.8	(272.7)	<0.0001
3.0 mg/kg	32	161.8	(223.5)	32	475.9	(301.1)	32	314.0	(187.7)	<0.0001

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CHr (pg)

Dose	Baseline n	Mean	(SD)	2-Week n	Mean	(SD)	Change from Baseline n	Mean	(SD)	p-value
1.5 mg/kg	24	31.2	(2.7)	24	32.4	(2.4)	23	1.3	(2.1)	0.0079
3.0 mg/kg	29	31.0	(2.9)	31	32.1	(2.2)	28	1.2	(2.7)	0.0297

Copied from Table 11.4-4
P-value was calculated using signed rank test.

HCRBC (%)

Dose	Baseline n	Mean	(SD)	2-Week n	Mean	(SD)	Change from Baseline n	Mean	(SD)	p-value
1.5 mg/kg	24	9.0	(10.8)	24	9.3	(12.8)	23	0.3	(8.0)	0.6502
3.0 mg/kg	29	7.6	(10.7)	31	7.3	(9.4)	28	-1.5	(9.0)	0.8701

Copied from Table 11.4-4
P-value was calculated using signed rank test.

As seen from table above, statistically significant improvement s in mean changes in Hct, TSAT, serum ferritin, and CHr concentrations compared to baseline value were observed 2 week after the last Ferrlecit infusion in both the 1.5 mg/kg and 3.0 mg/kg treatment groups. A non-significant increase in mean HCRBC levels occurred in the 1.5 mg/kg Ferrlecit treatment group. However, in the 3.0 mg/kg Ferrlecit treatment group, a non-significant decrease in mean HCRBC level occurred.

Treatment difference was observed for Serum Ferritin (ng/ml) (p=0.0003).

2.4 **Safety**

AEs were reported by 54 (81.8%) patients. The number of patients reporting AEs was similar between the 1.5 mg/kg (26 patients, 81.3%) and 3.0 mg/kg (28 patients, 82.4%) treatment groups.

The most common AEs occurring in ≥5%, were: hypotension (35%), headache (24%), hypertension (23%), tachycardia (17%), vomiting (11%), fever (9%), nausea (9%), abdominal pain (9%), pharyngitis (9%), diarrhea (8%), infection (8%), rhinitis (6%), and thrombosis (6%).

3. Reviewer's Comments and Evaluation

3.1 **Sample Size**

Per request from Ming Lu, M.D., medical reviewer, in November 2001, this reviewer computed the sample size for two treatment groups comparison. In my review it stated "Using power of 80% and significance level of 0.05, it was determined that 36 patients per treatment group would be required to detect a treatment difference of 1.0 g/dL. The calculation assumed that the standard deviation for the change in hemoglobin from baseline was 1.5 g/dL."

Due to the limit patient population for this disease, the sample size estimation was made based on using a paired t-test to detect a significant difference from zero for the change from baseline in Hgb. So, the sample size was inadequate for treatment group comparison.

3.2 **Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Variable**

3.2.1 **95% Confidence Interval**

It was unclear which method the sponsor used to compute 95% confidence interval for the responder. The 95% confidence intervals obtained by this reviewer using the Clopper-Pearson method were (21.1%, 61.3%) and (31.9%, 68.1%), for 1.5 mg/kg and 3.0 mg/kg Ferrlecit groups, respectively. They were slightly different from (20.8%, 59.2%) and (32.7%, 67.3%) obtained by the sponsor for 1.5 mg/kg and 30 mg/kg Ferrlecit groups, respectively.

3.2.2 **Analysis of Primary Efficacy Variable for Safety Population**

This reviewer performed analysis of primary efficacy variable for safety population.

The results of change in hemoglobin (Hgb) from baseline to 2 weeks after administration of the last Ferrlecit dose for safety population are given below.

Hgb (g/dL) Response and its Change from Baseline (Safety Population)

	Baseline		2-Week		Change from Baseline		
Dose	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	p-value
1.5 mg/kg	29	9.8 (2.3)	29	10.6 (2.4)	29	0.7 (1.34)	0.0049
3.0 mg/kg	34	9.4 (2.3)	34	10.2 (2.2)	34	0.8 (1.10)	0.0002

Compiled by this reviewer.
P-value was calculated using signed rank test.

As seen from table above, the results were similar to those obtained by sponsor for completer population. For safety population, mean Hgb concentrations were statistically greater 2 weeks after the last Ferrlecit infusion compared to baseline values in both the 1.5 mg/kg and 3.0 mg/kg treatment groups. The Hgb change between the two treatment groups was not statistically different 2 weeks after the final Ferrlecit infusion (p=0.4802, signed rank test). However, both treatment groups did not reach clinical significance.

3.3 **Reviewer's Comments on Sponsor's Analysis of Secondary Efficacy Variables**

3.3.1 **Responder to Treatment for Safety Population**

This reviewer performed analysis of responder to treatment for safety population.

The summary of results of responders to treatment 2 weeks after final Ferrlecit infusion is given below.

Summary of Responder to Treatment
(Safety Population)

Dose	Responder	95% Conf. Interval
1.5 mg/kg Ferrlecit	11/29 (38%)	(20.7%, 57.7%)
3.0 mg/kg Ferrlecit	16/34 (47%)	(29.8%, 64.9%)

Compiled by this reviewer.
95% CI was calculated using Clopper-Pearson method.

As seen from table above, the results were similar to those obtained by sponsor for completer population. For safety population, there was no statistically significant difference in the number of responders to treatment between the two treatment groups (p=0.4656).

3.3.2 Hct, TSAT, Serum Ferritin, CHr, and HCRBC Assessments

This reviewer performed analysis of Hct, TSAT, serum Ferritin, CHr, and HCRBC for safety population.

The results of change in Hct (%), TSAT (%), serum ferritin (ng/ml), CHr (pg), and HCRBC (5) from baseline to 2 weeks after administration of the last Ferrlecit dose for safety population are given below.

Change in Secondary Efficacy Variables from Baseline to
(Safety Population)

Hct (%)

	Baseline	2-Week	Change from Baseline	
Dose	n Mean (SD)	n Mean (SD)	n Mean (SD)	p-value
1.5 mg/kg	29 29.6 (7.3)	29 31.9 (7.1)	29 2.3 (4.1)	0.0058
3.0 mg/kg	34 28.2 (6.7)	34 30.9 (6.8)	34 2.7 (3.8)	0.0001

Compiled by this reviewer.
P-value was calculated using Signed Rank test.

TSAT (%)

	Baseline	2-Week	Change from Baseline	
Dose	n Mean (SD)	n Mean (SD)	n Mean (SD)	p-value
1.5 mg/kg	28 18.5 (10.3)	29 26.1 (14.0)	28 7. 9 (13.9)	0.0014
3.0 mg/kg	34 16.0 (10.5)	34 26.5 (16.1)	34 10.5 (13.5)	<0.0001

Compiled by this reviewer.
P-value was calculated using Signed Rank test

Serum Ferritin (ng/ml)

Dose	Baseline n	Baseline Mean (SD)	2-Week n	2-Week Mean (SD)	Change from Baseline n	Change from Baseline Mean (SD)	p-value
1.5 mg/kg	29	99.8 (133.6)	29	284.7 (327.5)	29	184.8 (260.7)	<0.0001
3.0 mg/kg	34	183.1 (262.6)	34	490.3 (321.6)	34	307.2 (184.0)	<0.0001

Compiled by this reviewer.
P-value was calculated using Signed Rank test

CHr (pg)

Dose	Baseline n	Baseline Mean (SD)	2-Week n	2-Week Mean (SD)	Change from Baseline n	Change from Baseline Mean (SD)	p-value
1.5 mg/kg	28	31.1 (3.1)	27	32.6 (2.4)	26	1.3 (2.1)	0.0009
3.0 mg/kg	31	30.9 (2.8)	32	32.1 (2.2)	29	1.2 (2.7)	0.0051

Compiled by this reviewer.
P-value was calculated using Signed Rank test

HCRBC (%)

Dose	Baseline n	Baseline Mean (SD)	2-Week n	2-Week Mean (SD)	Change from Baseline n	Change from Baseline Mean (SD)	p-value
1.5 mg/kg	28	9.2 (10.5)	27	10.1 (13.3)	26	1.6 (9.4)	0.8790
3.0 mg/kg	31	7.5 (10.3)	32	7.4 (9.3)	29	-1.2 (8.9)	0.9646

Compiled by this reviewer.
P-value was calculated using Signed Rank test

As seen from table above, the results were similar to those obtained by sponsor for completer population. For safety population, statistically significant improvement s in mean changes in Hct, TSAT, serum ferritin, and CHr concentrations compared to baseline value were observed 2 week after the last Ferrlecit infusion in both the 1.5 mg/kg and 3.0 mg/kg treatment groups. A non-significant increase in mean HCRBC levels occurred in the 1.5 mg/kg Ferrlecit treatment group. However, in the 3.0 mg/kg Ferrlecit treatment group, a non-significant decrease in mean HCRBC level occurred.

Treatment difference was observed for Serum Ferriitin (ng/ml) ($p<0.0001$).

C. Overall Summary and Recommendation

Study FR01006 showed for pediatric HD patients (≥2 years and <16 years of age), mean Hgb concentrations were statistically greater 2 weeks after the last Ferrlecit infusion compared to baseline values in both 1.5 mg/kg and 3.0 mg/kg Ferrlecit treatment groups for both completer and safety populations.

For secondary efficacy endpoints, for both completer and safety populations, statistically significant improvements in mean changes in Hct, TSAT, serum ferritin, and CHr concentrations compared to baseline value were observed 2 weeks after the last Ferrlecit infusion in both 1.5 mg/kg and 3.0 mg/kg Ferrlecit treatment groups. A non-significant increase in mean HCRBC levels occurred in the 1.5 mg/kg Ferrlecit treatment group. However, in the 3.0 mg/kg Ferrlecit treatment group, a non-significant decrease in mean HCRBC level occurred. Treatment difference was observed for Serum Ferriitin (ng/ml).

Table 1 Summary of Demographic and Baseline Characteristics --- Protocol FR01006
Safety Population

Characteristics	1.5 mg/kg Ferrlecit (N=32)	3.0 mg/kg Frrlecit (N=34)	Between Treatment p-value
Sex			0.4643
Male	15 (46.9%)	19 (55.9%)	
Female	17 (53.1%)	15 (44.1%)	
Race			0.2344
White	21 (65.6%)	26 (76.5%)	
Black	1 (3.1%)	3 (8.8%)	
Asian	1 (3.1%)	0 (0.0%)	
Hispanic	8 (25.0%)	4 (11.8%)	
Other Races	1 (3.1%)	1 (2.9%)	
Age (yr)			0.5864
Mean (SD)	12.3 (2.5)	12.0 (2.6)	
Age			0.2270
≥2 and ≤ 5 years	0 (0%)	0 (0%)	
≥6 and ≤ 12 years	16 (50.0%)	22 (64.7%)	
≥13 and ≤ 15 years	16 (50.0%)	12 (35.3%)	
Height (cm)			0.5089
Mean (SD)	138.6 (20.3)	135.4 (19.3)	
Weight (kg)			0.2057
Mean (SD)	37.7 (19.9)	32.5 (12.4)	

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P-values were obtained by this reviewer.
Chi-square test was used for sex and race. T-test was used for age, height, and weight..

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