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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/ Serial Number:	21882/S-015
Drug Name:	Exjade (Deferasirox)
Indication(s):	Treatment of iron overload
Applicant:	Novartis
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Keywords:

Baseline imbalance, blinding, covariate, dose response, logistic regression, multiple comparisons

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

The applicant submitted data and a final study report of a prospective, randomized, double-blind, placebo-controlled, phase II study to seek approval for deferasirox for the treatment of chronic iron overload in patients with non-transfusion-dependent thalassemia (NTDT) syndromes, and aged 10 years and older. Two different deferasirox starting doses (5 and 10 mg/kg/day) were evaluated. The placebo control comprised matching doses. The primary efficacy endpoint for the trial was the absolute change in Liver Iron Content (LIC) from baseline to Week 52. The study was to be claimed successful if the superiority of at least 1 deferasirox treatment group relative to placebo could be demonstrated with regard to the primary efficacy endpoint. Multiplicity was addressed by statistical test procedures controlling a 1-sided family wise type I error rate to 0.025 and 2-sided simultaneous 95% confidence intervals.

The protocol pre-specified primary efficacy analysis using the protocol pre-specified method of analysis of covariance (ANCOVA) with Dunnett's adjustment for multiple comparisons to the pooled placebo control group showed that deferasirox was statistically significant in favor for both the 5 mg/kg/day dose ($p=0.001$) and 10 mg/kg/day dose ($p<0.001$) relative to pooled placebo. However, FDA sensitivity analyses by comparing separately deferasirox 5 mg and 10 mg with each matching placebo using ANCOVA model with Tukey-Kramer multiple comparisons showed that deferasirox 5 mg is not statistically significantly different for the absolute change in LIC from baseline to Week 52 compared with placebo 5 mg. There is no clear evidence of dose dependence in response to deferasirox 10 mg in mean LIC change from baseline to Week 52.

Major efficacy issue and findings:

- The submission is based on only 1 randomized, placebo controlled phase II pivotal study. In general, FDA may accept a single pivotal study to support licensure if results show a highly statistically significant effect that is internally consistent across relevant subgroups. The results of the single pivotal trial must be sufficiently robust and compelling. However, in this submission, FDA sensitivity analyses can not confirm significant efficacy effect for the exjade 5 mg group, and this raised concern in the robustness of efficacy of exjade 5 mg.

- The study design was randomized, double-blind, placebo-controlled study. However, only treatment was blinded, and dose is not blinded. It is hard to control bias for dose effect for both groups.

- There are notably unbalanced baseline characteristics in this study. In particular, baseline LIC for treatment group was higher than placebo group.

- There are only 4 (2%) subjects in the study who are from United States.

- The primary efficacy analysis population that the sponsor used is Intent to Treat (ITT) with Last Observation Carry Forward (LOCF) imputation. However, the missing LIC value at 52 weeks for treatment group is as high as 20% in exjade 10 mg compared to 0 in placebo 10 mg. Such high rate of missing LIC value may undermine the reliability of efficacy results.

- The proposed labeling from the sponsor includes pediatric patients whose ages are greater or equal to 10 years old. However, only 13% of subjects in the study are younger than 18 years. Among all patients, 4% are 10-12 years old, 6% are 13-15 years old, and 2% are 16-17 years old.

2 INTRODUCTION

2.1 Overview

Deferasirox (Exjade) is an N-substituted bis-hydroxyphenyl-triazole, a representative of a new class of tridentate iron chelators that has been developed by Novartis for treating transfusional iron overload. Deferasirox is formulated as a dispersible tablet for oral suspension which facilitates administration of the appropriate quantity of drug substance to both pediatric and adult patients. Deferasirox is supplied as 125 mg, 250 mg and 500 mg tablets which can be dispersed in water, orange juice or apple juice. It was approved in the United States by the Food and Drug Administration (FDA) on 02-Nov-2005 for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older under New Drug Application (NDA) 21-882. Exjade is currently approved in more than 110 countries, including the European Union, Switzerland, for the treatment of chronic iron overload due to blood transfusions in adult and pediatric patients.

Magnetic resonance imaging (MRI) has been approved by device regulatory authorities in USA, Europe and Australia as a sensitive and specific experimental tool for assessing non-invasively hepatic iron overload and is used in this study.

This submission is designed to obtain approval of deferasirox (with a starting dose of 10 mg/kg/day) for the treatment of chronic iron overload in patients with non-transfusion-dependent thalassemia syndromes aged 10 years and older. The main difference between the proposed indicted population and the currently indicated population (patients with chronic iron overload due to blood transfusions) is that patients with NTDT require no or only occasional blood transfusions. They have iron overload mainly as a result of increased intestinal iron absorption. Because their rate of ongoing iron accumulation is lower than that of transfusion-dependent patients with thalassemia major, they require only intermittent chelation therapy with lower doses to reduce body iron below levels associated with morbidities.

This proposed new indication for deferasirox is based on a randomized, placebo-controlled study (Study CLCL760A2209). Study A2202/E, a phase I/II open-label, dose escalation study in hereditary hemochromatiosis HH patients, provides additional safety data (Table1).

Table 1 Clinical Development Programs

	Number of patients enrolled	Details	Status
Pivotal Study (2209)	166 in core 133 in extension	A randomized, doubled-blind, placebo-controlled, phase II study to evaluate efficacy and safety of deferasirox in non-transfusion-dependent thalassemia patiens with iron overload	Completed (core)
Supportive Study (2202/E)	Core and Extension	A phase I/II open-label, dose escalation trial to explore the safety and efficacy of exjade in patients with iron overload resulting from hereditary hemochromatiosis	Completed

Patients were considered to have completed the study after 12 months of study treatment. On completion of this one-year study patients could enter the Extension study. This was a prospective, open label, one-year extension study to evaluate long-term efficacy and safety of deferasirox in NTDT patients with iron overload. Patients from the active treatment arms of the Core study receive deferasirox for an additional year and patients from the placebo arms switch to deferasirox.

2.2 Data Sources

The applicant submitted this NDA including the data to the FDA CDER Electronic Document Room (EDR). The clinical study reports and datasets are located at the following location: \\CDSESUB1\EVSPROD\NDA021882\021882.ENX

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The analysis dataset was adequate and the reviewer was able to perform all analyses using the submitted data. No additional data submission was needed.

3.2 Evaluation of Efficacy

3.2.1 Study Objectives, Design and Endpoints

3.2.1.1 Study Objectives

Pivotal Study (2209)

Primary objective: to compare the efficacy of two regimens of deferasirox administration (starting doses of 5 and 10 mg/kg/day) in patients with non-transfusion-dependent thalassemia (NTDT) based on change in LIC from baseline after one year of treatment compared to placebo-treated patients.

Secondary objectives:

- To compare the efficacy of two regimens of deferasirox administration (starting doses of 5 and 10 mg/kg/day) in patients with NTDT based on change in LIC from baseline after 6 months of treatment with the placebo-treated patients.
- To compare change in serum ferritin over one year of treatment between deferasirox and placebo
- To evaluate the safety of both regimens of deferasirox versus placebo in NTDT patients
- To evaluate efficacy and safety of dose doubling
- To evaluate the last LIC value under doubled dose to the last value of LIC before the doubling of the dose
- To evaluate the relationship between serum ferritin and LIC
- To assess the change from baseline in hematological and iron metabolism parameter
- To evaluate the iron accumulation rate based on LIC assessment in NTDT patients treated with placebo.

Supportive Study (2202/E)

This study is aimed to prospectively assess the long-term efficacy and safety of deferasirox in non-transfusion-dependent thalassemia patients who completed the Core CICL670A2209.

Primary objective: to evaluate the number of patients reaching LIC < 5 mg Fe/g dw and to evaluate the long-term safety of deferasirox administration in patients with non-transfusion-dependent thalassemia.

3.2.1.2 Study Design

Pivotal Study (2209)

This was a prospective, randomized, double-blind, placebo-controlled, phase II study to evaluate efficacy and safety of deferasirox in NTDT patients with iron overload. Two different deferasirox starting doses (5 and 10 mg/kg/day) were evaluated. The placebo control was comprised of matching doses. Blinding only applied to deferasirox or placebo, as the blinding of dose was not feasible. The randomization ratio was 2:1:2:1 (5 mg/kg/day deferasirox/matching placebo dose/10 mg/kg/day deferasirox/matching placebo dose).

There was a 4 week screening period to determine if a patient was eligible and a blinded treatment period of 52 weeks either with deferasirox or placebo with starting doses of treatment regimens: 5 mg/kg/day p.o. (deferasirox or placebo) and 10 mg/kg/day p.o. (deferasirox or placebo).

Patients starting with 5 or 10 mg/kg/day were able to be dose escalated (up to 20 mg/kg/day) at month 6 based on the LIC value and change from baseline.

The number of patients planned for enrollment was 156 patients (52 patients in each deferasirox group and 26 patients in each of the corresponding placebo groups). A total of 166 patients were actually recruited at 27 sites in 9 countries. Due to uncertainty about standard deviation in LIC change from baseline at month 12, a blinded sample-size re-assessment was performed when 75% of the patients had been randomized and the result was presented to the Study Steering Committee (SSC) members on 13 and 14-Feb-2010. Based on 49 patients with a baseline and month 6 LIC measurements, the estimated standard deviation (SD) is lower than the assumed SD at time of the protocol, and hence the decision was taken that it was not necessary to increase the sample-size of the trial.

All patients underwent a preliminary evaluation period to assess eligibility that lasted for 4 weeks (Visit 1 and Visit 2). At the baseline visit (Visit 3, Day 1), patients whose eligibility was confirmed were randomized into one of the 4 treatments groups. Randomized patients were asked to come to the site for their weekly visits until Week 4, and every 4 weeks (4-weekly) until Week 24. Weekly visits from weeks 25 to 27 were done as follow-up visits after dose-escalation, and 4-weekly from Week 28 to Week 48. Week 52 was the end of the study (EOS).

A data monitoring committee (DMC) regularly reviewed safety data and advised Novartis on study continuation and/or any changes to the protocol.

Patients who completed the double-blind treatment phase were give the option of entering a 52-week open-label extension phase of the study (reported separately) to obtain more information on long-term safety and efficacy data of deferasirox in this indication.

Supportive Study (2202/E)

This is a prospective, open label, one-year extension study to evaluate long-term efficacy and safety of deferasirox in non-transfusion-dependent thalassemia patients with iron overload. Patients from the active treatment arms of the core study will receive deferasirox for an additional year and patients from the placebo arms will switch to deferasirox. The treatment goal is to normalize body iron level assessed by LIC. As in the core study, the study drug is continued until LIC is <3 mg Fe/g dw and then it is interrupted. Once a sufficient amount of iron is accumulated, which is reflected by LIC

3.2.1.3 Study Endpoints

Pivotal Study (2209)

The primary efficacy endpoint was the change in LIC from baseline after 12 months of treatment with study drug.

The secondary efficacy endpoint was the change in LIC from baseline after 6 months of treatment with study drug.

Supportive Study (2202/E)

Liver iron content (LIC) assessment by MRI: LIC will be measured after six month and at the end of the extension study using a validated R2 MRI technique.

Serum ferritin assessment: serum ferritin level will be measured monthly or quarterly by a central laboratory.

3.2.1.4 Statistical hypothesis

Pivotal Study (2209)

For pairwise comparisons of the two deferasirox means (μ_{5mg} and $\mu_{10\,mg}$) against the placebo mean μ_{pla}, the null hypotheses are:

H0 5mg: $\mu_{5mg} = \mu_{pla}$ (no effect deferasirox 5 mg with regard to change in LIC) and
H0 10mg: $\mu_{10mg} = \mu_{pla}$ (no effect deferasirox 10 mg with regard to change in LIC)

These hypotheses are tested against the respective one–sided alternative hypotheses

H1 5mg: $\mu_{5mg} < \mu_{pla}$ (no effect deferasirox 5 mg with regard to change in LIC) and
H1 10mg: $\mu_{10mg} < \mu_{pla}$ (no effect deferasirox 10 mg with regard to change in LIC)

3.2.1.5 Sample Size Calculation

Pivotal Study (2209)

The sample size has been determined to obtain 90% power for showing superiority of at least one deferasirox treatment group over placebo with respect to change to baseline in LIC at week 52. With the multiplicity adjustment and the following assumptions:

- One-sided family wise type I error probability of α=0.025
- A true mean decrease of 3 mg in LIC at week 52 compared to placebo
- A true standard deviation (SD) of 4 mg for change to baseline in LIC at week 52
- A sample size of 46 patients in each deferasirox group and 23 in each matching placebo group (138 patients in total) is sufficient to achieve 90% power to reject at least one of the two null hypotheses comparing deferasirox to placebo.
- Considering a potential of 10% patients without any post-baseline LIC value , the sample size needs to be increase to 52 patients for each deferasirox group and to 26 for each placebo group (156 patients in total)

Due to uncertainty of the initial estimate for standard deviation in LIC change to baseline at week 52, a blinded sample size re-assessment is scheduled when 75% (n=117) of the patients will have been randomized. As recruitment is targeted for one year, week 52 LIC data will not be available at that point in time. Therefore, the total SD estimate for the available pooled week 24 data (without any treatment group unbinding) will be used as a surrogate SD estimate of the LIC change to baseline at week 52. (Kieser and Friede 2000) and (Friede and Kieser 2006) reported sufficient accuracy of the total SD estimate (in particular as differences in means are expected to be smaller in week 24 as in week 52) and inflation of type I error rate by such blinded sample-size re-assessment as negligible ($\leq$ 0.0001). The total SD estimate was used to recalculate power for the currently planned sample size and the updated sample size needed to achieve a power of 90%. These results would be shared with the study's Steering Committee deciding upon increase of sample size or accepting the potential loss in power without any sample size increase. Reduction of sample size is not an option.

An analysis to assess the patient-level standard deviation were presented to SSC members on 12 and 14 –Feb -2010. Based on 49 patients with a baseline and month 6 LIC measurements the SD of absolute change from baseline was estimated as (3.22 vs. 4.00), the decision was taken that it was not necessary to increase the sample-size of the trial.

Reviewer's Comment:
The reviewer sent an information request to the applicant asking for detailed report for the sample size re-assessment and the results. Responses were provided by the applicant. There were no major deficiencies in sponsor's responses.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

Pivotal Study (2209)

A total of 166 patients were randomized and treated in the study. A total of 148 (89.2%) subjects completed the study (Table 2).

Table 2 Patient Disposition

	Deferasirox 5 mg/kg/day N=55 n (%)	Deferasirox 10 mg/kg/day N=55 n (%)	Placebo 5 mg/kg/day N=28 n (%)	Placebo 10 mg/kg/day N=28 n (%)	Placebo Any dose N=56 n (%)
Treated with study drug	55 (100.0)	55 (100.0)	28 (100.0)	28 (100.0)	56 (100.0)
Completed study	48 (87.3)	49 (89.1)	25 (89.3)	26 (92.9)	51 (91.1)
Discontinued study	7 (12.7)	6 (10.9)	3 (10.7)	2 (7.1)	5 (8.9)
Adverse event(s)	2 (3.6)	3 (5.5)	0	1 (3.6)	1 (1.8)
Subject withdrew consent	1 (1.8)	2 (3.6)	2 (7.1)	0	2 (3.6)
Lost to follow-up	3 (5.5)	1 (1.8)	0	0	0
Abnormal laboratory value(s)	0	0	0	1 (3.6)	1 (1.8)
Protocol deviation	1 (1.8)	0	1 (3.6)	0	1 (1.8)

Source: Applicant's Clinical Study Report Table 10-1

Reviewer's Comments:
The rate of discontinuation of the study was slightly higher in the deferasirox groups (12.7% in deferasirox 5 mg group and 10.9% in deferasirox in 10 mg), compared to placebo groups (10.7% in placebo 5 mg and 7.1% in placebo 10 mg). The rate of adverse events was higher in the deferasirxo group (3.6% and 5.5 % of patients), compared to placebo groups (0 and 3.6% of patients). The rate of lost to follow up was higher in the deferasirox groups (5.5% and 1.8% of patients), compared to placebo groups (0%).

The full analysis set (FAS), the per protocol set (PPS) and the safety set comprised 166 (100%), 130 (78.3%) and 166 (100.0%) subjects, respectively (Table 3)

Table 3 Summary of Number of Patients in Analysis Sets

	Deferasirox 5 mg/kg/day N=55 n (%)	Deferasirox 10 mg/kg/day N=55 n (%)	Placebo 5 mg/kg/day N=28 n (%)	Placebo 10 mg/kg/day N=28 n (%)	Placebo Any dose N=56 n (%)	All patients N=166 n (%)
Full Analysis Set (FAS)	55 (100.0)	55 (100.0)	28 (100.0)	28 (100.0)	56 (100.0)	166 (100.0)
Per Protocol Set (PPS)	41 (74.5)	44 (80.0)	23 (82.1)	22 (78.6)	45 (80.4)	130 (78.3)
Safety Set	55 (100.0)	55 (100.0)	28 (100.0)	28 (100.0)	56 (100.0)	166 (100.0)

Source: Applicant's Clinical Study Report Table 11-1

Table below shows the reviewer's summary of demographic and baseline characters. The median age in the 5 mg/kg/day deferasirox, 10 mg/kg/day deferasirox and placebo groups were 33.1, 31.7, 31.9 and 30.9 years respectively (Table 4)

Table 4 Reviewer's Summary of Demographic and Baseline Characteristics

Variable	Total (N=166)	Deferasirox5 (N=55)	Deferasirox10 (N=55)	Placebo5 (N=28)	Placebo10 (N=28)
AGE					
1=<18 years	21 (13%)	6 (11%)	7 (13%)	2 (7%)	6 (21%)
2>=18 years	145 (87%)	49 (89%)	48 (87%)	26 (93%)	22 (79%)
1=Male	89 (54%)	29 (53%)	29 (53%)	15 (54%)	16 (57%)
2=Female	77 (46%)	26 (47%)	26 (47%)	13 (46%)	12 (43%)
1=Caucasian	94 (57%)	31 (56%)	30 (55%)	17 (61%)	16 (57%)
2=Asian	69 (42%)	23 (42%)	24 (44%)	11 (39%)	11 (39%)
3=Black	2 (1%)	1 (2%)	1 (2%)	0 (0%)	0 (0%)
4=Other	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)
Std Dev	845.7	804.9	684.4	1121.0	921.9

Variable	Total (N=166)	Deferasirox5 (N=55)	Deferasirox10 (N=55)	Placebo5 (N=28)	Placebo10 (N=28)
Median	991.8	988.0	1014.5	1188.0	882.0
1<=7 mg Fe/g dw	31 (19%)	10 (18%)	8 (15%)	5 (18%)	8 (29%)
2=5-7 mg Fe/g dw	77 (46%)	31 (56%)	26 (47%)	10 (36%)	10 (36%)
3>7-15 mg Fe/d dw	57 (34%)	14 (25%)	21 (38%)	12 (43%)	10 (36%)
4>15 mg Fe/d dw	1 (1%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)
0=No	21 (13%)	6 (11%)	5 (9%)	5 (18%)	5 (18%)
1=Yes	145 (87%)	49 (89%)	50 (91%)	23 (82%)	23 (82%)
1>300-500 ug/L	17 (10%)	5 (9%)	4 (7%)	5 (18%)	3 (11%)
2>500-1000 ug/L	67 (40%)	24 (44%)	23 (42%)	7 (25%)	13 (46%)
3>1000 ug/L	82 (49%)	26 (47%)	28 (51%)	16 (57%)	12 (43%)
Yes		29 (53%)	31 (56%)	14 (50%)	14 (50%)

Reviewer's Comments:
Some of the baseline characteristics were slightly different across treatment groups. The rate of age <18 years was notably different in the deferasirox groups (11% and 13% of patients), compared to placebo groups (7% and 21%). The means of LIC at baseline were lower in the deferasirox 5 mg (13.1 mg Fd/g dw)group, compared to placebo 5 mg group (17.8 mg Fd/g dw). The means of serum ferritin (SF) at baseline was slightly lower in the deferasirox 5 mg group (1140.7), compared to placebo 5 mg group (1320.9). The rate of prior transfusion (N) was slightly lower in the deferasirox 10 mg group (9% of patients), compared to placebo 10 mg group (18% of patients). The rate of splenectomy (Y) was slightly higher in the deferasirox 10 mg group (56% of patients), compared to placebo 10 mg group (50% of patients).

3.2.3 Statistical Methodologies

Pivotal Study (2209)

3.2.3.1 Primary Efficacy Analysis (Absolute change of LIC at week 52)

The study was to be considered successful if the superiority of at least 1 deferasirox treatment group (starting dose of 5 or 10 mg/kg/day) relative to placebo could be demonstrated with regard to the primary efficacy endpoint. Multiplicity was addressed by statistical test procedures controlling a 1-sided family-wise type I error rate to 0.025 and 2-sided 95% confidence intervals.

Analysis of covariance (ANCOVA) was performed with 1-sided t-tests using Dunnett's adjustment for multiple comparisons to the placebo control group. The family-wise type I error rate was set to 0.025 so that an adjusted p-value of at most 0.025 led to the rejection of the respective null hypothesis. The ANCOVA model for the change in LIC included the treatment group (5 mg/kg/day deferasirox starting dose, 10 mg/kg/day deferasirox starting dose, placebo) as factor and baseline LIC as covariate. As a result, the primary efficacy results were presented adjusted for baseline.

The following estimates were provided:

- For each of the 3 treatment groups the least squares means of change in LIC and ordinary 2-sided 95% confidence interval.
- For each of the 2 deferasirox groups, the least squares means of the difference against placebo with 2-sided simultaneous 95% confidence intervals using the Dunnett adjustment

In case both deferasirox arms were statistically superior to placebo (and only in this case), the 2 deferasirox groups were to be compared by means of a 2-sided t-test at a significance level of 5%. Because this test was only performed if both deferasirox arms were statistically superior to the control, no adjustment of the type I error (α) was required. The point estimate for the difference in means between two deferasirox groups were to be provided together with ordinary 2-sided 95% confidence interval.

3.2.3.2 Secondary Efficacy Analysis

The absolute change from baseline LIC at Week 24 was analyzed in the same way as the primary efficacy variable on the Full Analysis Set (FAS).

For serum ferritin quarterly change from baseline, a mixed effect model was fitted.

The correlation of LIC versus serum ferritin at baseline was assessed as well as the correlation of relative change in LIC versus relative change in serum ferritin at week 24 and week 25. An ANCOVA was performed for the difference in LIC between baseline and Week 52 including treatment group, age category, gender and transfusion during the study (no, yes) as factors and baseline LIC and the fourth quarter change in serum ferritin as covariates in order to assess the proportion of treatment effect explained by change in serum ferritin. A similar ANCOVA model

for the difference in LIC between baseline and Week 24 was performed with the second quarter change in serum ferritin as covariate.

Supportive Study (2202/E)

This is an open-label single-arm trial. The data will be presented in a descriptive manner.

3.2.4 Results and Conclusions

Pivotal Study (2209)

3.2.4.1 Primary Efficacy Results

Pre-Specified Efficacy Analyses Results:
Pre-specified efficacy analyses results showed that change in LIC from baseline to Week 52 was statistically significantly in favor for both the 5 mg/kg/day dose and the 10 mg/kg/day dose (Dunnett's adjusted p=0.001 and p<0.001 respectively) of deferasirox compared to placebo. Change in LIC from baseline to Week 52 was statistically significantly in favor for the 10 mg/kg/day compared to the 5 mg/kg/day group (p=0.009) (Table 5)

Table 5 Summary of Analysis of Covariance for the change in LIC from Baseline to Week 52 (FAS)

	Deferasirox 5 mg/kg/day (N=51)	Deferasirox 10 mg/kg/day (N=54)	Placebo Any dose (N=54)
LIC change from baseline Least square mean (95% CI)	 -1.95 (-2.94, -0.96)	 -3.80 (-4.76, -2.85)	 0.38 (-0.59, 1.34)
Difference Deferasirox-Placebo Least square mean (95% CI)	 -2.33 (-3.89, -0.76) p=0.001	 -4.18 (-5.71, -2.64) P<0.001	
Difference Deferasirox 10-5 Least square mean (95% CI)		-1.85 (-3.22, -0.48) 0.009	

The ANCOVA model described above was also carried out on Per-Protocol Set (PPS) by sponsor. In the PPS, where patients who had major protocol deviation or received transfusion during the study were excluded, the differences between the deferasirox (5 mg/kg/day, 10 mg/kg/day) and placebo treatment groups were also both statistically significant favoring deferasirox treated groups (Dunnett's adjusted p-value<0.001 for both), and the least square means of absolute change of LIC from baseline to Week 52 were -2.48 mg Fe/g dw [95% CI: -3.59, -1.39], -4.30 mg Fe/g dw [95% CI:-5.35, -3.25] and 0.46 mg Fe/g dw[95CI:-0.58, 1.51] in the 5 mg and 10 mg deferasirox and placebo treatment groups respectively (Table 6).

Table 6 Analysis of Covariance of Absolute Change in LIC between Baseline and Week 52 (PPS)

	ICL670 5 mg/kg (N=41)	ICL670 10 mg/kg (N=44)	Placebo (N=45)
Least squares mean	-2.48	-4.30	0.46
Standard error	0.554	0.533	0.528
95% confidence interval	-3.58, -1.39	-5.35, -3.25	-0.58, 1.51
Difference ICL670 - Placebo			
Least squares mean	-2.95	-4.76	-
Standard error	0.768	0.751	-
95% confidence interval (1)	-4.66, -1.23	-6.44, -3.08	-
p-value (2)	<.001	<.001	-
Difference ICL670 10 mg/kg - ICL670 5 mg/kg			
Least squares mean	-	-1.82	-
Standard error	-	0.768	-
95% confidence interval	-	-3.34, -0.30	-
p-value (3)	-	0.019	-

Estimates were obtained from an ANCOVA model for absolute change in LIC between baseline and Week 52 with treatment as factor and baseline LIC as covariate.
(1) two-sided simultaneous confidence intervals using Dunnett adjustment
(2) one-sided p-value with Dunnett's adjustment testing the hypothesis that the mean decrease in LIC under ICL670 is not greater than under placebo. Critical alpha-level: 0.025
(3) two-sided p-value testing the hypothesis that the change in LIC is identical in the two ICL670 groups. Critical alpha-level: 0.05
The last available post-baseline LIC before Week 52 was carried forward if no LIC value was available at Week 52.
Only patients with both baseline and at least one post-baseline value were included for this analysis.

Source: Applicant's Clinical Study Report Table 14.2-1.2

Reviewer's Analyses Results and Comments

The ANOVA model was also carried out on observed population without LOCF imputation. The results showed that change in LIC from baseline to Week 52 was statistically significantly different in favor for both deferasirox 5mg/kg/day and deferasirox 10 mg/kg/day compared to pooled placebo with Dunnett's adjusted p=0.0084 and p<0.001 respectively (Table7).

Table 7 Reviewer's Analysis of Variance of Absolute Change in LIC between Baseline and Week 52 using Dunnett Adjustment (FAS Observed)

	Deferasirox 5 mg N=55	Deferasirox 10 mg 10 mg N=55	Placebo Any doses N=56
Change from baseline			
N (%)	48 (87%)	44 (80%)	54 (96.45)
LS Mean	-1.8	-3.8	0.26
95% CI	-2.79, -0.77	-4.84, -2.72	-0.69, 1.21
Diff Deferasirox-Placebo			
LS Mean	-2.03	-4.04	

95% CI p-value	-3.61, -0.46 0.0084	-5.65, -2.43 <0.0001	
Diff Defferasirox10-5mg LS Mean 95% CI p-value		 -2.00 -3.48, -0.52 0.009	

The primary efficacy analysis was the comparison of the exjade 5 or 10 mg/kg/day to pooled placebo. There is a concern of placebo effect. For example, taking 5 mg/kg or 2 mg/kg of placebo may give a different result. The reviewer performed sensitivity analysis using ANCOVA model with Tukey-Cramer method for multiplicity adjustment instead of Dunnet adjustment. Dunnet described an alternative alpha error adjustment when 2 groups are compared to the same control group and the method is less conservative. However, Tukey-Cramer method for multiplicity adjustment is more conservative when difference among samples size are bigger. Since our analyses were comparison for each exjade 5 or 10 mg group to its matching placebo, with randomization ratio of 2:1, using Tukey-Cramer method is appropriate for such analysis.

Table 8 shows the reviewer's sensitivity analysis results for the primary efficacy endpoint using Tukey-Kramer adjustment for observed population. The results showed that change in LIC from baseline to Week 52 was statistically significant in favor of the 10 mg/kg/day dose with difference in LS mean of -4.8 and p-value less than 0.0001. However, change in LIC from baseline to Week 52 was not statistically significant different comparing the 5mg/kg/day dose and its matching placebo, with difference in LS mean of -1.2 and p-value of 0.50.

Table 8 Analysis of Variance of Absolute Change in LIC between Baseline and Week 52 using Tukey-Kramer Adjustment (FAS Observed)

	Deferasirox 5 mg N=55	Deferasirox 10 mg 10 mg N=55	Placebo 5mg N=28	Placebo 10mg N=28
Change from baseline N (%) LS Mean 95% CI p-value	 48 (87%) -1.8 -2.78, -0.77 0.0006	 44 (80%) -3.8 -4.83, -2.73 <0.0001	 26 (92.86%) -0.6 -1.94, 0.79 0.40	 28 (100%) 1.0 -0.28, 2.35 0.12
Diff Deferasirox-matching Placebo LS Mean 95% CI p-value	 --1.2 -3.4, 1.03 0.50	 -4.8 -7.0, -2.6 <0.0001		
Diff Defferasirox10-5mg LS Mean		 -2.00		

95% CI p-value		-3.91, -0.09 0.04		

We also performed several confirmative analyses for comparing 5 mg vs. its placebo. The methods we used include nonparametric Kruskal-Wallis test, t-test with multiplicity correction using either Bonferroni or Sidak, in which both methods came with same critical p-values of 0.0125. The p-values of all these confirmative analyses are greater than critical value, indicating that there is no statistically significant difference in the LIC mean change between exjade 5 mg and its matching placebo group.

Table 9 Confirmative analyses for comparing 5 mg vs. its placebo

Method	Two sided p-value	One sided p-value	Critical p-value with multiplicity correction (one-sided)
Kruskal-Wallis (KW)	0.09	0.05	Bonferroni=0.0125
T test	0.10	0.05	
ANOVA	0.1135	0.06	Sidak=0.0125

Figure 1 and 2 show the reviewer's summary of mean LIC over time , and absolute LIC change from baseline for the 5 groups, exjade 5 mg, exjade 10 mg, placebo 5 mg , placebo 10 mg and pooled placebo group. The exjade 5 mg group has the highest baseline LIC value compared with other groups. There is no significant LIC change from baseline for all 5 groups at week 24.

Figure 1 Reviewer's Summary of Mean LIC over Time

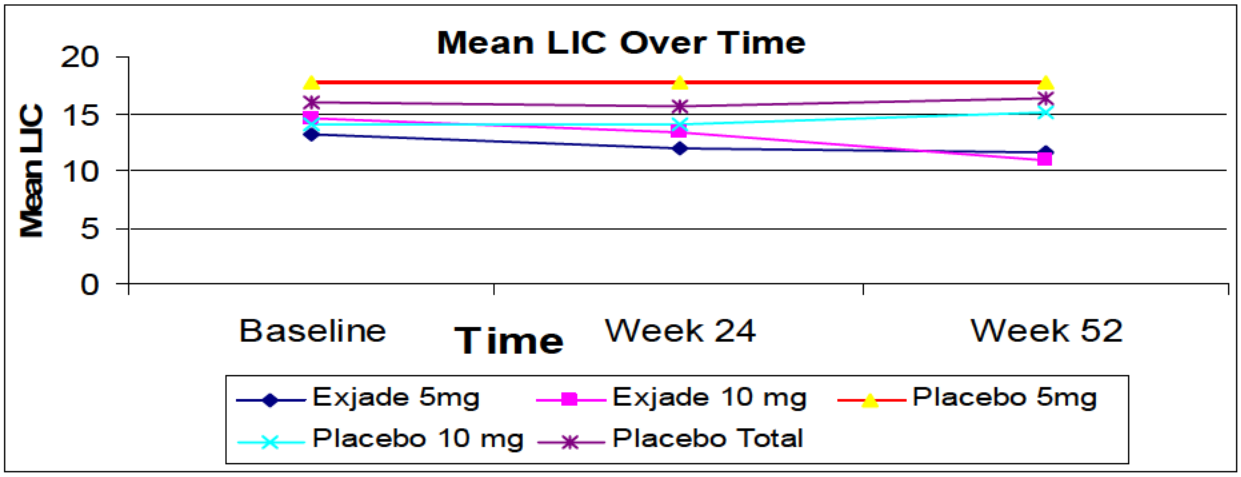


Figure 2 Absolute Change in LIC over Time

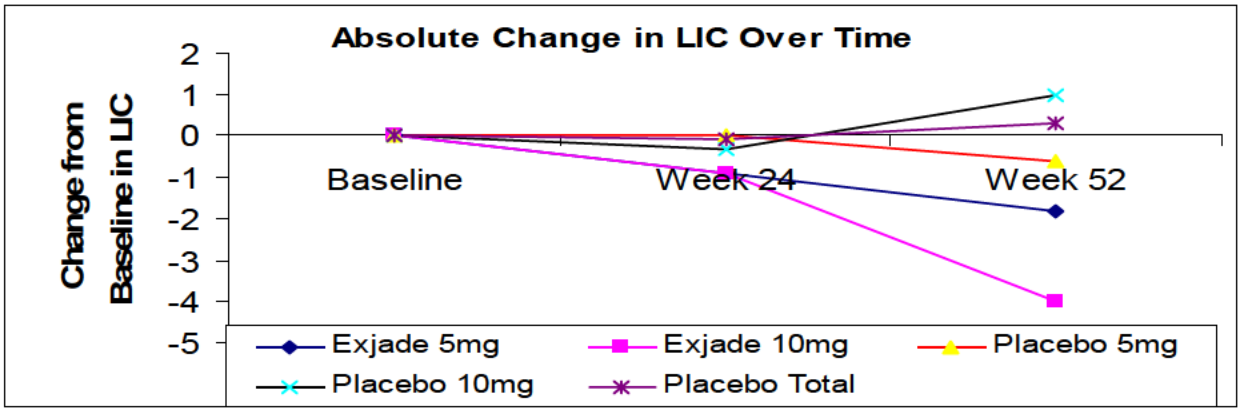
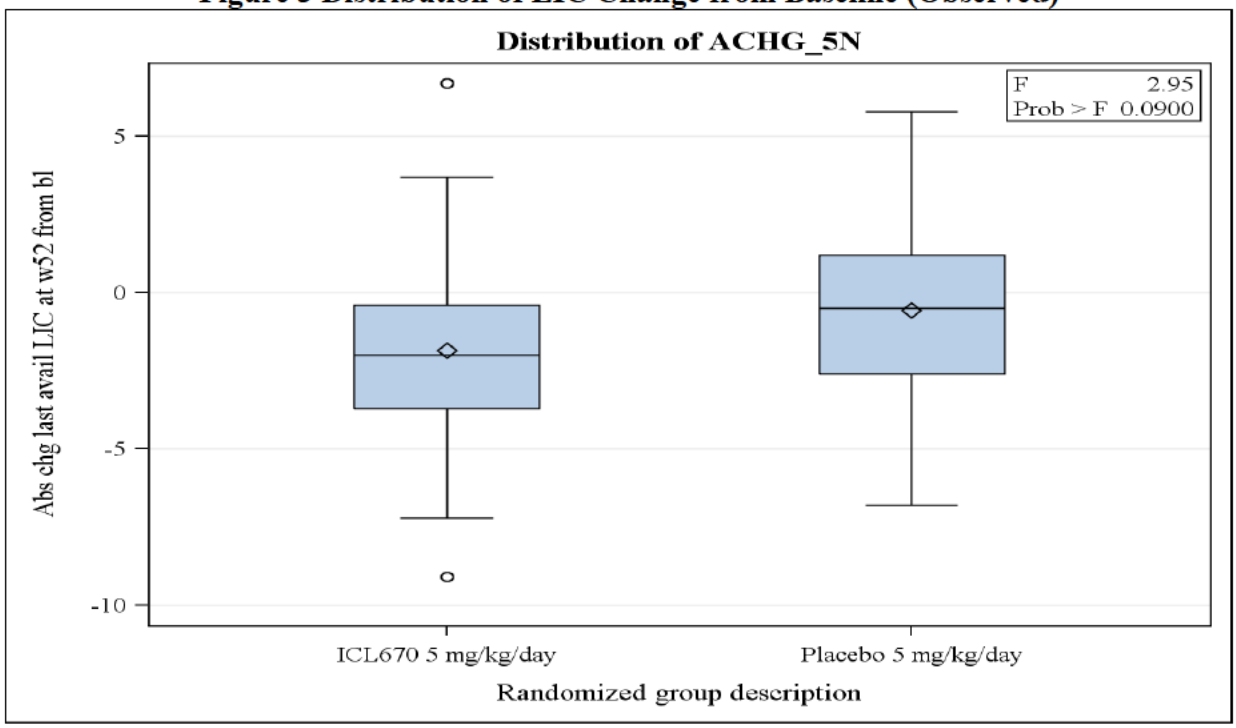


Figure 3 shows the distribution of LIC change from baseline for exjade 5 mg compared to placebo 5 mg. There is no significant difference between these 2 groups. There is no significant difference in the distributions of LIC change from baseline to week 52 between these 2 groups.

Figure 3 Distribution of LIC Change from Baseline (Observed)



The major limitation for such analysis is the comparison to each matching placebo instead of pooled placebo reduces the power for detecting a significant effect. However, the descriptive analysis and graphic analysis also showed lack of robustness in efficacy for the exjade 5 mg for the primary efficacy endpoint. In addition, the baseline LIC was higher for the exjade group

compared to the placebo group, which may make the results in favor of placebo group. All these results raised the question that if exjade 5 mg can effectively change the LIC at 52 weeks.

3.2.4.2 Secondary Efficacy Results

Reviewer's Comments

The secondary efficacy analyses were not powered when the study was designed. The applicant did not pre-specify adjustment for multiplicity for the secondary efficacy endpoints analyses. (b) (4).

3.2.4.2.1 Change of LIC from baseline to Week 24

Reviewer's Analysis and Comments:

The analysis results showed that the least square mean of absolute change in LIC between baseline and Week 24 was greater for the deferasirox treated patients than placebo-treated patients; however, this difference did not reach statistical significance for either 5 mg or 10 mg deferasirox treatment groups compared to the placebo group (Table 8)

Table 10 Reviewer's Analysis of Variance of Absolute Change in LIC between Baseline and Week 24 using Dunnett Adjustment (FAS)

	Deferasirox 5 mg N=55	Deferasirox 10 mg 10 mg N=55	Placebo Any doses N=56
Change from baseline			
N (%)	49 (89%)	48 (87%)	51 (91%)
LS Mean	-0.93	-0.90	-0.18
95% CI	-1.81, -0.05	-1.79, -0.01	-1.05, 0.68
Diff Deferasirox-Placebo			
LS Mean	-0.74	-0.71	
95% CI	-2.13, 0.65	-2,11, 0.69	
p-value	0.39	0.42	

3.2.4.2.2 Change in serum ferritin between baseline and fourth quarter

The sponsor's analysis of variance of absolute change in serum ferritin between baseline and the fourth quarter was greater following deferasirox treatment compared to the placebo group; the 95% CI 10 mg deferasirox group and the 5 mg deferasirox group was (-217.92, 15.31) (Table 9)

Table 11 Absolute Change in Serum Ferritin (ug/L) between Baseline and Second Fourth Quarter (FAS)

	Deferasirox 5 mg/kg/day	Deferasirox 10 mg/kg/day	Placebo Any dose
	(N=55)	(N=55)	(N=56)
n	55	55	56
Least squares mean	-120.69	-222.00	114.54
Standard error	41.759	41.759	41.384
95% confidence interval	-203.15, -38.24	-304.46, -139.54	32.83, 196.26
Difference deferasirox - Placebo			
Least squares mean	-235.24	-336.54	-
Standard error	58.791	58.791	-
95% confidence interval (1)	-365.99, -104.49	-467.29, -205.79	-
p-value (2)	<.001	<.001	-
Difference deferasirox 10 mg/kg/day - deferasirox 5 mg/kg			
Least squares mean	-	-101.31	-
Standard error	-	59.056	-
95% confidence interval	-	-217.92, 15.31	-
p-value (3)	-	0.088	-

The estimates for the 4th quarter were obtained from a repeated measurements model with treatment and quarter as factors, and treatment*quarter interaction.
(1) two-sided simultaneous confidence intervals using Dunnett adjustment
(2) one-sided p-value with Dunnett's adjustment testing the hypothesis that the mean decrease in serum ferritin is not greater under deferasirox than under placebo. Critical **alpha**-level: 0.025
(3) two-sided p-value testing the hypothesis that the change in serum ferritin is identical in the two deferasirox groups. Critical **alpha** -level: 0.05
The last available quarter was carried forward if no value was available for any quarter.

Source: Applicant's Clinical Study Report Table 11-13

Reviewer's Analysis Results and Comments

The reviewer's summary of the absolute change in serum ferritin between baseline and different quarters are presented in Table 12. Decrease in the serum ferritin from baseline to the second quarter was greater in the 10 mg group than in the 5 mg group. This dose effect was also observed for the fourth quarter where the decrease in serum ferritin was approximately 50% higher in the 10 mg group than in the 5 mg group. In the placebo group serum ferritin was increased from the baseline to the second and the fourth quarter.

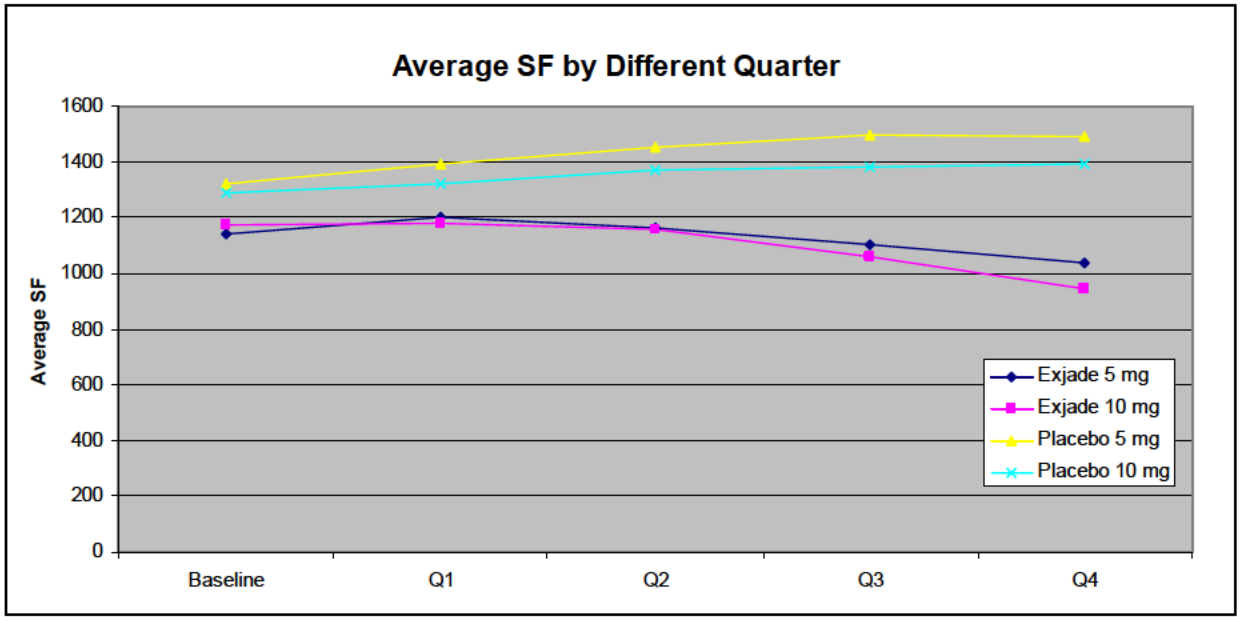
Table 12 Reviewer's Summary of the Mean of Absolute Change in Serum Ferritin

Randomized group description	N Obs	Label	N	Mean	Std Dev	Minimum	Maximum
ICL670 10 mg/kg/day	55	Serum ferritin at baseline (ug/L)	55	1173.89	684.37	341.50	4223.50
		Q1 Serum ferritin abs change	55	6.04	190.22	-289.50	759.00
		Q2 Serum ferritin abs change	54	-17.75	368.81	-832.67	1561.50
		Q3 Serum ferritin abs change	51	-136.41	360.10	-1040.50	882.75
		Q4 Serum ferritin abs change	50	-249.16	389.36	-1406.75	987.97
ICL670 5 mg/kg/day	55	Serum ferritin at baseline (ug/L)	55	1140.69	804.93	369.50	5608.50
		Q1 Serum ferritin abs change	55	62.25	265.03	-530.50	687.83
		Q2 Serum ferritin abs change	52	8.20	244.44	-519.83	1056.33
		Q3 Serum ferritin abs change	50	-56.22	250.91	-670.50	592.25
		Q4 Serum ferritin abs change	51	-130.47	260.56	-839.00	375.83
Placebo 10 mg/kg/day	28	Serum ferritin at baseline (ug/L)	28	1289.35	921.94	303.50	3365.00
		Q1 Serum ferritin abs change	28	30.93	199.75	-296.17	610.67
		Q2 Serum ferritin abs change	28	81.94	332.43	-620.00	1159.33
		Q3 Serum ferritin abs change	27	117.80	274.79	-232.50	1049.75
		Q4 Serum ferritin abs change	27	127.98	256.68	-304.17	835.33
Placebo 5 mg/kg/day	28	Serum ferritin at baseline (ug/L)	28	1320.87	1121.04	329.70	6418.50
		Q1 Serum ferritin abs change	28	71.50	294.57	-267.50	1249.50
		Q2 Serum ferritin abs change	28	130.97	332.21	-267.00	1414.83
		Q3 Serum ferritin abs change	26	130.75	195.05	-185.00	743.67
		Q4 Serum ferritin abs change	26	129.31	247.30	-344.00	701.25

Table 13 Average Serum Ferritin by Different Quarter

Randomized group description	N Obs	Label	N	Mean	Std Dev	Minimum	Maximum
ICL670 10 mg/kg/day	55	Serum ferritin at baseline (ug/L)	55	1173.89	684.37	341.50	4223.50
		Q1 Serum ferritin average	55	1179.92	724.96	373.33	4467.67
		Q2 Serum ferritin average	54	1157.24	828.84	284.33	4356.33
		Q3 Serum ferritin average	51	1056.69	709.94	216.67	4136.67
		Q4 Serum ferritin average	50	942.83	685.47	134.00	4204.00
ICL670 5 mg/kg/day	55	Serum ferritin at baseline (ug/L)	55	1140.69	804.93	369.50	5608.50
		Q1 Serum ferritin average	55	1202.94	869.36	347.00	5647.00
		Q2 Serum ferritin average	52	1165.05	863.86	349.33	5539.00
		Q3 Serum ferritin average	50	1104.51	751.33	323.75	4995.00
		Q4 Serum ferritin average	51	1038.04	727.08	291.33	4860.25
Placebo 10 mg/kg/day	28	Serum ferritin at baseline (ug/L)	28	1289.35	921.94	303.50	3365.00
		Q1 Serum ferritin average	28	1320.28	938.15	271.33	3675.67
		Q2 Serum ferritin average	28	1371.29	986.07	236.33	4224.33
		Q3 Serum ferritin average	27	1383.19	1034.25	248.00	4114.75
		Q4 Serum ferritin average	27	1393.36	1059.52	288.75	3900.33
Placebo 5 mg/kg/day	28	Serum ferritin at baseline (ug/L)	28	1320.87	1121.04	329.70	6418.50
		Q1 Serum ferritin average	28	1392.37	1354.20	248.00	7668.00
		Q2 Serum ferritin average	28	1451.84	1386.81	255.00	7833.33
		Q3 Serum ferritin average	26	1495.16	1210.64	440.00	6751.50
		Q4 Serum ferritin average	26	1493.73	1150.55	460.00	6400.33

Figure 4 Average Serum Ferritin by Different Quarter



3.2.4.2.3 Effect of deferasirox dose increase on absolute change in LIC

Reviewer's Analyses and Comments:
Based on clinical reviewer's request, this reviewer did analysis by including average weight based dose in the ANCOVA model. For comparison of exjade 5 mg to its matching placebo, the p-value is 0.016, indicating average weight based dose significantly impacts the model. However, average weight based dose is not significant for the comparison of LIC change between exjade 10 mg and placebo 10 mg. The reviewer also did linear regression of LIC change versus the average weight based dose, by exjade 5 mg and 10 mg, and the results show that dose has significant impact on LIC change for exjade 5mg, and no significant impact for exjade 10 mg (Table 14).

Table 14 LIC Change between Baseline and Week 52 by Average Actual Daily Dose

LIC Change	Exjade >0-<7.5	Exjade ≥7.5-≤12.5	Exjade ≥12.5-≤17.5
Mean Exjade 5 mg	-1.54	-3.76	0
Mean Exjade 10 mg	-5.9	-3.4	-4.18

3.2.4.2.4 Evaluation of the relationship between serum ferritin and LIC

Reviewer's Analyses and Comments:

Correlation analysis was performed for baseline serum ferritin and baseline LIC (r=0.639, p<0.0001), for change in serum ferritin from baseline to Week 52 and change in LIC from

baseline to Week 52 (r=0.3108, p=0.0001). The results indicated that serum ferritin and LIC are correlated (Table 15), but that level of correlation between changes in serum ferritin and LIC is small (so that one is not greatly predictive of the other at patient level).

Table 15 Analysis of the Relationship between Change in Serum Ferrtin and Change in LIC

Source	DF	Type III SS	Mean Square	F Value	Pr > F
LIC Change	1	3198952.926	3198952.926	15.76	0.0001
AGE	1	10904.583	10904.583	0.05	0.8171
SEX	1	8538.936	8538.936	0.04	0.8378
SF_Baseline	1	1614199.929	1614199.929	7.95	0.0056

Supportive Study (2202/E)

As the Agency received the data for extension study on December 06, 2012 from the applicant, the review of the extension study will be provided in the Addendum.

3.3 Evaluation of Safety

See clinical review report

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Pivotal Study (2209)

4.1 Gender, Race, Age, and Geographic Region

Reviewer's Subgroup Analyses and Comments

Absolute change in LIC was analyzed by gender, race, age and geographic region by this reviewer.

Table 16 shows the distribution of treatment group by gender. For male, there are 29 (53%) subjects in both deferasirox 5mg group and deferasirox 10 mg group, and 31 (55%) subjects in the pooled placebo group. For female, there are 26 (47%) subjects in both deferasirox 5mg group and deferasirox 10 mg group, and 25 (45%) subjects in the pooled placebo group. The distributions of gender in different treatment groups are similar.

Table 16 Gender distribution in each group

	Deferasirox 5 mg N=55	Deferasirox 10 mg mg N=55	Placebo Any doses N=56
Male N (%)	29 (53%)	29 (53%)	31 (55%)
Female N (%)	26 (47%)	26 (47%)	25 (45%)

Table 17 shows reviewer's analysis of variance of absolute change in LIC between baseline and week 52 using Dunnett adjustment for male subjects.

Table 17 Reviewer's Analysis of Variance of Absolute Change in LIC between Baseline and Week 52 using Dunnett Adjustment (FAS Sex=Male)

Male	Deferasirox 5 mg N=29	Deferasirox 10 mg 10 mg N=29	Placebo Any doses N=31
Change from baseline			
N (%)	27 (93%)	28 (97%)	30 (97%)
LS Mean	-1.07	-3.61	-0.19
95% CI	-2.44, -0.30	-4.84, -2.72	-0.49, 1.11
Diff Deferasirox-Placebo			
LS Mean	-0.87	-4.04	
95% CI	-3.01, 1.26	-5.53, -1.3	
p-value	0.56	<0.0009	

Table 18 shows reviewer's analysis of variance of absolute change in LIC between baseline and week 52 using Dunnett adjustment for female subjects.

Table 18 Reviewer's Analysis of Variance of Absolute Change in LIC between Baseline and Week 52 using Dunnett Adjustment (FAS Sex=Female)

Female	Deferasirox 5 mg N=26	Deferasirox 10 mg 10 mg N=26	Placebo Any doses N=25
Change from baseline			
N (%)	24 (92%)	26 (100%)	24 (96%)
LS Mean	-2.74	-3.96	0.83
95% CI	-4.22, -1.26	-5.38, -2.54	-0.65, 2.30
Diff Deferasirox-Placebo			
LS Mean	-3.56	-4.79	
95% CI	-5.93, -1.20	-7.11, -2.47	
p-value	0.002	<0.0001	

Table 19 shows the distribution of race for different treatment groups.

Table 19 Distribution of Race in each group

	Deferasirox 5 mg N=55	Deferasirox 10 mg 10 mg N=55	Placebo Any doses N=56
Caucasian	31 (56%)	30 (55%)	33 (59%)
Asian	23 (42%)	24 (44%)	22 (39%)
Black	1 (2%)	1 (2%)	0 (0)

Table 20 shows reviewer's analysis of variance of absolute change in LIC between baseline and week 52 using Dunnett adjustment for Caucasian.

Table 20 Reviewer's Analysis of Variance of Absolute Change in LIC between Baseline and Week 52 using Dunnett Adjustment (FAS Race=Caucasian)

Caucasian	Deferasirox 5 mg N=31	Deferasirox 10 mg 10 mg N=30	Placebo Any doses N=33
Change from baseline			
N (%)	27 (87%)	29 (97%)	32 (97%)
LS Mean	-1.40	-4.67	0.44
95% CI	-2.73, -0.08	-5.95, -3.39	-0.78, 1.65
Diff Deferasirox-Placebo			
LS Mean	-1.84	-5.11	
95% CI	-3.88, 0.19	-7.10, -3.11	
p-value	0.08	<0.0001	

Table 21 shows reviewer's analysis of variance of absolute change in LIC between baseline and week 52 using Dunnett adjustment for Asian.

Table 21 Reviewer's Analysis of Variance of Absolute Change in LIC between Baseline and Week 52 using Dunnett Adjustment (FAS Race=Asian)

Asian	Deferasirox 5 mg N=23	Deferasirox 10 mg 10 mg N=24	Placebo Any doses N=22
Change from baseline			
N (%)	23 (100%)	24 (100%)	21 (95%)
LS Mean	-2.3	-2.64	0.02
95% CI	-3.9, -0.72	-4.20, -1.08	-1.65, 1.68
Diff Deferasirox-Placebo			
LS Mean	-2.33	-2.66	
95% CI	-4.93, 0.27	-5.24, -0.08	
p-value	0.08	0.04	

Table 22 shows the distribution of age groups in different treatment groups..

Table 22 Age Distribution by treatment group

Age	Placebo Any doses N=56	Deferasirox 5 mg N=55	Deferasirox 10 mg N=55	Total
<18 Years	8 14.29	6 10.91	7 12.73	21
>=18 Years	48 85.71	49 89.09	48 87.27	145
Total	56	55	55	166

Table 23 shows reviewer's analysis of variance of absolute change in LIC between baseline and week 52 using Dunnett adjustment for subjects <18 years old.

Table 23 Reviewer's Analysis of Variance of Absolute Change in LIC between Baseline and Week 52 using Dunnett Adjustment (FAS Age<18 Years)

<=18 Years	Deferasirox 5 mg N=6	Deferasirox 10 mg 10 mg N=7	Placebo Any doses N=8
Change from baseline			
N (%)	6 (100%)	7 (100%)	8 (95%)
LS Mean	-1.55	-4.30	-0.15
95% CI	-3.51, 0.41	-6.11, -2.49	-1.85, 1.55
Diff Deferasirox-Placebo			
LS Mean	-1.40	-4.15	
95% CI	-4.37, 1.57	-6.99, -1.31	
p-value	0.44	0.0048	

Table 24 shows reviewer's analysis of variance of absolute change in LIC between baseline and week 52 using Dunnett adjustment for subjects >=18 years old.

Table 24 Reviewer's Analysis of Variance of Absolute Change in LIC between Baseline and Week 52 using Dunnett Adjustment (FAS Age>=18 Years)

>=18 Years	Deferasirox 5 mg N=49	Deferasirox 10 mg 10 mg N=48	Placebo Any doses N=48
Change from baseline			
N (%)	45 (92%)	47 (98%)	46 (96%)
LS Mean	-1.89	-3.70	-0.33
95% CI	-3.01, -0.78	-4.80, -2.61	-0.77, 1.43
Diff Deferasirox-Placebo			
LS Mean	-2.22	-4.03	

95% CI p-value	-4.00, -4.45 0.01	-5.79, -2.28 <0.0001	

Table 25 shows distribution of geographic region by different treatment groups.

Table 25 Distribution of Geographic Region by Study Group

Frequency Col Pct	Placebo Any doses N=56	Deferasirox 5 mg N=55	Deferasirox 10 mg N=55	Total
GBR	2 3.57	3 5.45	3 5.45	8
GRC	4 7.14	4 7.27	4 7.27	12
ITA	11 19.64	10 18.18	10 18.18	31
LBN	10 17.86	10 18.18	9 16.36	29
MYS	3 5.36	4 7.27	3 5.45	10
THA	19 33.93	18 32.73	18 32.73	55
TUR	5 8.93	5 9.09	6 10.91	16
TWN	0 0.00	0 0.00	1 1.82	1
USA	2 3.57	1 1.82	1 1.82	4
Total	56	55	55	166

Table 26 shows reviewer's analysis of variance of absolute change in LIC between baseline and week 52 using Dunnett adjustment for subjects enrolled in Thailand. Subgroup analyses for other regions were not performed due to small sample sizes.

Table 26 Reviewer's Analysis of Variance of Absolute Change in LIC between Baseline and Week 52 using Dunnett Adjustment (FAS Region=THA)

THA	Deferasirox 5 mg N=18	Deferasirox 10 mg 10 mg N=18	Placebo Any doses N=19
Change from baseline N (%) LS Mean 95% CI	 18 (100%) -2.18 -3.9, -0.72	 18 (100%) -3.00 -4.79, -1.21	 18 (95%) 0.17 -1.65, 1.68
Diff Deferasirox-Placebo LS Mean	 -2.36	 -3.17	

95% CI p-value	-5.23, 0.52 0.12	-6.05, -0.30 0.03	

4.2 Other Special/Subgroup Populations

Table 27 shows distribution of underlying diseases of the patients by treatment group.

Table 27 Distribution of Underlying Disease of the Patient

Frequency **Col Pct**	Placebo Any doses N=56	Deferasirox 5 mg N=55	Deferasirox 10 mg N=55	**Total**
Beta-thalassemia	33 58.93	32 58.18	30 54.55	95
Alpha-thalassemia	8 14.29	5 9.09	9 16.36	22
HbE beta-thalassemia	15 26.79	18 32.73	16 29.09	49
Total	56	55	55	166

Table 28 shows reviewer's analysis of variance of absolute change in LIC between baseline and week 52 using Dunnett adjustment for patients with beta-thalassemia at the baseline.

Table 28 Reviewer's Analysis of Variance of Absolute Change in LIC between Baseline and Week 52 using Dunnett Adjustment (FAS Beta-thalassemia)

Beta-thalassemia	Deferasirox 5 mg N=32	Deferasirox 10 mg 10 mg N=30	Placebo Any doses N=33
Change from baseline N (%) LS Mean 95% CI	 28 (88%) -1.18 -2.39, 0.03	 29 (97%) -4.53 -5.72, -3.34	 32 (97%) 0.72 -0.41, 1.86
Diff Deferasirox-Placebo LS Mean 95% CI p-value	 -1.91 -3.79, -0.03 0.05	 -5.26 -7.12, -3.39 <0.0001	

Table 29 shows reviewer's analysis of variance of absolute change in LIC between baseline and week 52 using Dunnett adjustment for patients with HbE beta-thalassemia at the baseline.

Table 29 Reviewer's Analysis of Variance of Absolute Change in LIC between Baseline and Week 52 using Dunnett Adjustment (FAS HbE beta-thalassemia)

HbE beta-thalassemia	Deferasirox 5 mg N=18	Deferasirox 10 mg 10 mg N=16	Placebo Any doses N=15
Change from baseline			
N (%)	18 (100%)	16 (100%)	15 (100%)
LS Mean	-2.11	-3.16	-0.19
95% CI	-4.05, -0.17	-5.22, -1.10	-2.32, 1.93
Diff Deferasirox-Placebo			
LS Mean	-1.91	-2.97	
95% CI	-5.18, 1.34	-6.32, 0.38	
p-value	0.31	<0.09	

Table 30 shows the distribution of any-prior-transfusion by treatment group.

Table 30 Distribution of Any-Prior-Transfusion (Yes/No) by Study Group

Any Prior Transfusion	Placebo Any doses N=56	Deferasirox 5 mg N=55	Deferasirox 10 mg N=55	**Total**
No	10 17.86	6 10.91	5 9.09	21
Yes	46 82.14	49 89.09	50 90.91	145
Total	56	55	55	166

Table 31 shows reviewer's analysis of variance of absolute change in LIC between baseline and week 52 using Dunnett adjustment for patients with prior transfusion at baseline. Subgroup analysis was not performed for patients without prior transfusion at baseline due to small sample size.

Table 31Reviewer's Analysis of Variance of Absolute Change in LIC between Baseline and Week 52 using Dunnett Adjustment (FAS Prior Transfusion=Yes)

Prior transfusion Yes	Deferasirox 5 mg N=49	Deferasirox 10 mg 10 mg N=50	Placebo Any doses N=46
Change from baseline			
N (%)	46 (94%)	49 (98%)	45 (98%)
LS Mean	-1.67	-3.67	0.17
95% CI	-2.73, -0.60	-4.71, -2.64	-0.90, 1.25
Diff Deferasirox-Placebo			
LS Mean	-1.84	-3.85	

95% CI p-value	-3.55, -0.13 0.03	-5.53, -2.16 <0.0001	

Table 32 shows distribution of splenctomy status by treatment group.

Table 32 Distribution of Splenctomy Status by Different Treatment Group

Splenectomized	Placebo Any doses N=56	Deferasirox 5 mg N=55	Deferasirox 10 mg N=55	**Total**
No	28 50.00	26 47.27	24 43.64	78
Yes	28 50.00	29 52.73	31 56.36	88
Total	56	55	55	166

Table 33 shows reviewer's analysis of variance of absolute change in LIC between baseline and week 52 using Dunnett adjustment for patients without splenectomy at baseline.

Table 33 Reviewer's Analysis of Variance of Absolute Change in LIC between Baseline and Week 52 using Dunnett Adjustment (FAS Splenctomized=No)

Splenectomized No	Deferasirox 5 mg N=26	Deferasirox 10 mg N=26	Placebo Any doses N=28
Change from baseline N (%) LS Mean 95% CI	 25 (96%) -2.76 -4.19, -1.34	 24 (92%) -3.93 -5.38, -2.47	 26 (93%) 0.17 -1.23, 1.56
Diff Deferasirox-Placebo LS Mean 95% CI p-value	 -2.93 -5.19, 0.67 0.009	 -4.09 -6.38, -1.80 0.0003	

Table 34 shows reviewer's analysis of variance of absolute change in LIC between baseline and week 52 using Dunnett adjustment for the patients with splenctomy at baseline.

Table 34 Reviewer's Analysis of Variance of Absolute Change in LIC between Baseline and Week 52 using Dunnett Adjustment (FAS Splenctomized=Yes)

Splenectomized Yes	Deferasirox 5 mg N=29	Deferasirox 10 mg N=31	Placebo Any doses N=28
Change from baseline N (%) LS Mean 95% CI	 26 (87%) --0.98 -2.40, 0.44	 30 (97%) -3.66 -4.99, -2.34	 28 (100%) 0.35 -1.02, 1.71

Diff Deferasirox-Placebo LS Mean 95% CI p-value	 -1.32 -3.56, 0.91 0.31	 -4.01 -6.16, -1.86 0.0001	

Table 35 shows distribution of dose escalation by treatment group

Table 35 Distribution of Dose Escalation (Yes/No) by Treatment Group

Dose Escalation	Placebo Any doses N=56	Deferasirox 5 mg N=55	Deferasirox 10 mg N=55	Total
No	26 46.43	29 52.73	30 54.55	85
Yes	30 53.57	26 47.27	25 45.45	81
Total	56	55	55	166

Reviewer's Comments

The statistical power for detecting the same magnitude of treatment effect may be insufficient in those subgroup analyses unless the precision of subgroup estimate has been considered properly in planning the sample size or the variability of the response is sufficiently small in the subgroup. Therefore, we recommend that those subgroup analyses are only exploratory and suggestive, but not conclusive.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Key statistical issues and findings that impact on the demonstration of efficacy/safety are as follows:

- The submission is based on only 1 randomized, placebo controlled phase II pivotal study. In general, FDA would accept a single pivotal study to support licensure if results show a highly statistically significant effect that is internally consistent across relevant subgroups. The results of the single pivotal trial must be sufficiently robust and compelling. However, in this submission, FDA sensitivity analyses can not confirm significant efficacy effect for the exjade 5 mg group, and this raised concern in the robustness of efficacy of exjade 5 mg.

- The study design was randomized, double-blind, placebo-controlled study. However, only treatment was blinded, and dose is not blinded. It is hard to control bias for dose effect for both groups.

- There are notably unbalanced baseline characteristics in this study. In particular, baseline LIC for treatment group was higher than placebo group.

- There are only 4 (2%) subjects in the study are from United States.

- The primary efficacy analysis population that the sponsor used is ITT with LOCF imputation. However, the missing LIC value at 52 weeks for treatment group is as high as 20% in exjade 10 mg compared to 0 in placebo 10 mg. Such high rate of missing LIC value may undermine the reliability of efficacy results.

- The proposed labeling from the sponsor includes pediatric patients whose ages are greater or equal to 10 years old. However, only 13% of subjects in the study are younger than 18 years. Among all patients, 4% are 10-12 years old, 6% are 13-15 years old, and 2% are 16-17 years old.

5.2 Conclusions and Recommendations

The applicant submitted data and a final study report of a prospective, randomized, double-blind, placebo-controlled, phase II study to seek approval for deferasirox for the treatment of chronic iron overload in patients with non-transfusion-dependent thalaseemia (NTDT) syndromes, and aged 10 years and older. Two different deferasirox starting doses (5 and 10 mg/kg/day) were evaluated. The placebo control comprised matching doses. The primary efficacy endpoint for the trial was the absolute change in LIC from baseline to Week 52. The study was to be claimed successful if the superiority of at least 1 deferasirox treatment group relative to placebo could be demonstrated with regard to the primary efficacy endpoint. Multiplicity was addressed by statistical test procedures controlling a 1-sided family wise type I error rate to 0.025 and 2-sided simultaneous 95% confidence intervals.

The protocol pre-specified primary efficacy analysis using protocol pre-specified method of analysis of covariance (ANCOVA) with Dunnett's adjustment for multiple comparisons to the pooled placebo control group showed that deferasirox was statistically significant in favor for both the 5 mg/kg/day dose ($p=0.001$) and 10 mg/kg/day dose ($p<0.001$) relative to pooled placebo. However, FDA sensitivity analyses by comparing separately deferasirox 5 mg and 10 mg with each matching placebo using ANCOVA model with Tukey-Kramer multiple comparisons showed that deferasirox 5 mg is not statistically significantly different for the absolute change in LIC from baseline to Week 52 compared with placebo 5 mg. There is no clear evidence of dose dependence in response for deferasirox 10 mg in mean LIC at Week 52.

5.3 Labeling Recommendations


(b) (4)

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/s/

QING XU
12/19/2012

MARK D ROTHMANN
12/19/2012
I concur

THOMAS E GWISE
12/19/2012
I concur