CLINICAL REVIEW

Application Number(s)	**NDA 021882 S-015**
Application Type	Efficacy Supplement
Priority or Standard	Standard
Submit Date(s)	12/23/2011
Received Date(s)	12/23/2011
PDUFA Goal Date	1/23/2013
Review Completed	12/12/2012
Office / Division	Office of Hematology and Oncology Products / Division of Hematology Products
Primary Reviewer	Donna Przepiorka, MD, PhD
Team Leader	Albert Deisseroth, MD, PhD
Established Name	**Deferasirox**
(Proposed) Trade Name	**Exjade®**
Therapeutic Class	Tridentate iron chelator
Applicant	Novartis
Formulation(s)	Tablet for Oral Suspension 125 mg, 250 mg, 500 mg
Dosing Regimen	Initial daily dose is 10 mg/kg orally once daily for an LIC $\leq$15 mg Fe/g dw and 20 mg/kg once daily for an LIC >15 mg Fe/g dw
Indication(s)	Treatment of chronic iron overload
Intended Population(s)	Non-transfusion-dependent thalassemia patients greater than 10 years of age with an LIC $\geq$5 mg Fe/g dw

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AE	Adverse Event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST	Aspartate aminotransferase
CFR	Code of Federal Regulations
CI	Confidence interval
CTD	Common Technical Document
D10	Deferasirox 10 mg/kg/day arm
D5	Deferasirox 5 mg/kg/day arm
ECG	Electrocardiograph
EU	European Union
FDA	Food and Drug Administration
GCP	Good clinical practice
GDF15	Growth differentiation factor 15
GGT	Gamma glutamyl transferase
Hgb	Hemoglobin
HH	Hereditary hemochromatosis
HIF	Hypoxia-inducible transcription factors
HLGT	High level group term
HLT	High level term
LIC	Liver Iron Concentration
MDS	Myelodysplastic syndrome
Mg Fe/g dw	Milligrams iron per gram dry weight
NTDT	Non-Transfusion Dependent Thalassemia
PK	Pharmacokinetic
PSUR	Periodic Safety Update Report
PT	Preferred term
SAE	Serious adverse event
SCD	Sickle cell disease
SF	Serum ferritin
SMQ	Standardized MedDRA query
sNDA	Supplemental New Drug Application
SOC	System Organ Class
TI	Thalassemia Intermedia
TM	Thalassemia Major
WBC	White blood cell
x LLN	Times the lower limit of normal
x ULM	Times the upper limit of normal

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of deferasirox under Subpart H (21 CFR 314.510) for the treatment of chronic iron overload in patients 10 years of age and older with non-transfusion-dependent thalassemia syndromes (NTDT) [redacted] (b) (4) and a liver iron concentration (LIC) ≥5 mg Fe/g dry weight (dw). Confirmation of clinical benefit is required.

Approval is supported by the results in the Core and Extension protocols of Study A2209 showing the target LIC (<5 mg Fe/g dw by R2 magnetic resonance imaging (MRI)) was achieved by 41-51% of the subjects with NTDT treated for one year with deferasirox at 10 mg/kg/day when the baseline LIC was ≤15 mg Fe/g dw, and that there was a dose-dependent absolute reduction in LIC for those subjects with a baseline LIC >15 mg Fe/g dw. It remains to be confirmed in postmarketing studies that subjects with the higher baseline LIC achieve the target LIC with longer term therapy, to determine how best to maintain the target LIC once it is achieved, and to verify safety with long-term use in the intended population.

1.2 Risk Benefit Assessment

Table 1: Benefit-Risk Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Patients with NTDT have chronic iron overload resulting from disordered iron metabolism. • Iron-related complications increase with total body iron burden. • In a retrospective analysis, the risk of complications was lower in patients who received chelation therapy and in those whose liver iron concentration was ≤6 mg Fe/g dw.	Patients with NTDT may develop substantial morbidities from chronic iron overload. Those at highest risk for such morbidities can be identified and offered treatment to reduce the iron load.
Unmet Medical Need	• There are no approved therapies for prevention of the complications of chronic iron overload in patients with NTDT.	There is a need for a chelation therapy with evidence-based instructions for safe and effective use in patients with NTDT.
Clinical Benefit	• Study A2209 included a 1-year, blinded, placebo-controlled dose-finding Core protocol and a 1-year, open-label Extension protocol. • An LIC <5 mg Fe/g dw was achieved by 41-51% of subjects treated with deferasirox 10 mg/kg/day when the baseline LIC was <15 mg Fe/g dw. • Only 10% of subjects with a baseline LIC >15 mg Fe/g dw achieved the target LIC even with deferasirox at 20 mg/kg/day, but the mean absolute reduction in LIC over one year was -9.1 mg Fe/g dw at that dose.	Deferasirox 10 mg/kg/day for one year is effective in reducing the body iron burden in patients with NTDT and a baseline LIC <15 mg Fe/g dw. A dose of 20 mg/kg/day for two years is expected to achieve success for those with higher baseline LICs. Additional study is required to assess the efficacy of intermittent maintenance therapy and to confirm clinical benefit.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risks	• The adverse events reported were similar to those experienced by patients with transfusional iron overload. • No new adverse events were identified in the NTDT population. • The risk of adverse events was not increased in those subjects who achieved and LIC <3 mg Fe/g dw.	The overall short-term safety profile is acceptable for the NTDT population. Targeting an LIC <3 mg Fe/g dw to stop treatment appears safe. Additional studies are required to assess the safety of long-term use and the effects on growth and development in children.
Risk Management	• The current labeling includes extensive warnings and precautions that address the known serious complications associated with use of deferasirox in patients with transfusional iron overload. • Measurement of LIC by R2 MRI was validated, including for patients with NTDT. • Serum ferritin had only a modest correlation with LIC in the NTDT population.	The warnings and precautions currently in the labeling also apply to the NTDT population. Instructions for use will be guided by LIC as measured by biopsy or R2 MRI rather than solely by ferritin.

Background: Mechanistic studies show that patients with NTDT have increased iron absorption from the gastrointestinal tract with subsequent deposition in the liver and other tissues resulting from disordered iron metabolism driven by ineffective erythropoiesis. Cross sectional cohort studies revealed that the NTDT subpopulation suffers from serious iron-related complications, such as diabetes mellitus, hypothyroidism, hypogonadism and bone abnormalities, and the risk of these complications increases with age. It may take several decades for these complications to become manifest. There are no approved agents for the treatment of patients with NTDT.

The cross sectional cohort studies also showed that patients receiving chelation therapy had a lower risk of disease-related complication. An LIC $\geq$ 6 mg Fe/g dw was identified as the optimal cut point to identify patients with an increased rate of complications. This analysis has been used in practice to establish a specific LIC as a surrogate for later disease-related complications in patients with NTDT. The reviewer acknowledges that there is some uncertainty in the applicability of the results of this analysis, since the population in the cross sectional cohort study was limited to patients with thalassemia intermedia, and there have been no additional studies performed to confirm the validity of LIC $\geq$ 6 mg Fe/g dw as a predictor of later complications.

Clinical Development Program: The evidence to support approval of deferasirox comes from Study A2209 which included two protocols, Core and Extension, for treatment of patients with NTDT over the age of 10 years with an LIC $\geq$5 mg Fe/g dw by R2 MRI. The Core protocol was a blinded, randomized trial of one year duration that compared two dose levels of deferasirox (5 mg/kg/day and 10 mg/kg/day) and placebo; after six months of therapy, the dose could be doubled if there was no response. The Extension protocol was an open-label, single-arm trial of one year duration for subjects treated on the Core protocol (including cross-over of subjects from the placebo arm). Treatment in the Extension protocol was assigned to largely 10 mg/kg/day or 20 mg/kg/day depending on the LIC at enrollment, and after six months of therapy, the dose could be increased if the LIC was >7 and there was no response to therapy in the prior 6 months. The Core protocol accrued 166 subjects; 130 of them were also treated on the Extension

protocol, including 48 who crossed over from the placebo arm to active treatment. Only 113 subjects treated on the Extension protocol had a baseline LIC ≥5 mg Fe/g dw.

Efficacy: A full summary of efficacy is provided in Section 6. The primary efficacy endpoint in the Core protocol was the absolute change in LIC from baseline to week 52. This was a positive study. However, since it was unclear what specific magnitude of change in LIC was clinically important, this endpoint could not be used to assess clinical benefit. The primary efficacy endpoint in the Extension protocol was the proportion of patients who achieved an LIC <5 mg Fe/g dw. Since this target LIC was less than the threshold identified in a cross sectional analysis as correlating with an increased risk of later complications in the patients with thalassemia intermedia, it was concluded that the endpoint of achieving an LIC <5 mg Fe/g dw was reasonably likely to predict a clinical benefit.

In the Core protocol, 23 of 110 (21%, 95% CI 14-30%) subjects treated with deferasirox for one year achieved the target LIC vs 2 of 56 (4%, 95% CI <1-12%) subjects treated with placebo. In the Extension protocol, 39 of the 113 (35%, 95% CI 26-44%) evaluable subjects treated with deferasirox for one year achieved the target LIC. The efficacy of deferasirox was also supported by two published pilot studies which reported 14-30% of patients with NTDT achieved the target LIC with one year of treatment with deferasirox.

Table 2: Efficacy Outcomes for Study A2209

	Initial Dose			
	Placebo	**Deferasirox 5 mg/kg/day**	**Deferasirox 10 mg/kg/day**	**Deferasirox 20 mg/kg/day**
Number Achieving LIC <5 mg Fe/g dw at Week 52 (%)				
Core Protocol				
All patients[1]	2/56 (4%)	8/55(15%)	15/55 (27%)	-
Baseline LIC ≤15	2/34 (6%)	8/41(20%)	14/34 (41%)	-
Baseline LIC >15	0/22 (0%)	0/14 (0%)	1/21 (5%)	-
Extension Protocol[2]				
All patients[1]	-	3/5 (60%)	31/65 (48%)	5/43 (12%)
Baseline LIC ≤15	-	3/5 (60%)	31/61 (51%)	1/4 (25%)
Baseline LIC >15	-	-	0/4 (0%)	4/39 (10%)
Mean Absolute LIC Change (95% CI) at Week 52 (mg Fe/g dw)				
Core Protocol[3]	+0.3	-1.9	-3.8	-
	(-0.7. +1.2)	(-2.7, -1.0)	(-4.9, -2.6)	-
Extension Protocol[3]	-	-1.5	-2.8	-9.1
	-	(-3.7 to +0.7)	(-3.4 to -2.2)	(-11.0 to -7.3)

[1]The median baseline LIC (range) was 12.1 (2.6-49.1) mg Fe/g dw in the Core Protocol and 10.9 (1.2 – 46.4) mg Fe/g dw in the Extension Protocol.
[2]Includes only the 113 subjects with baseline LIC ≥5 mg Fe/g dw from 130 subjects treated.
[3]Includes all evaluable subjects in the respective protocols.

Further subset analyses demonstrated that achieving the target LIC depended on both the baseline LIC and the dose of deferasirox. The results in Table 2, which shows the efficacy

outcomes by baseline LIC and starting dose of deferasirox, suggest that a starting dose of 10 mg/kg/day is effective when the baseline LIC is ≤15 mg Fe/g dw.

Achievement of the target LIC was numerically best using the 20 mg/kg/day dose when the LIC was >15 mg Fe/g dw, although even this dose was successful in only 10% of such subjects. The reduction in LIC over one year (mean -9.1 mg Fe/g dw) suggests that two years of therapy at 20 mg/kg/day would be successful for those with a high baseline LIC, but this remains to be confirmed in a prospective clinical trial.

Safety: A full summary of safety is provided in Section 7. The safety dataset include 158 subjects with NTDT treated with deferasirox who were on study A2209 for a median of 23 months (range <1-27 months). Dose increases were prespecified during the course of treatment, and exposure varied by subject over time. The dose of 10 mg/kg/day was used for some period of time by more than 80% of the subjects; this dose was also used the longest by more than 50% of the subjects. The safety data set also includes 56 subjects treated with placebo for one year.

There were no deaths. There were two serious adverse events (rash and hepatotoxicity) considered related to deferasirox. Table 3 shows all suspected adverse events reported in 2% or more of treated subjects.

Table 3: Suspected Adverse Events For Study A2209

Preferred Term	Extension Protocol (n=130)		Core Protocol			
			Treated (n=110)		Placebo (n=56)	
	n	%	n	%	n	%
Any Event	**27**	**21**	**32**	**29**	**9**	**16**
Diarrhoea	7	5	5	5	1	2
Blood creatinine increased	5	4	2	2	0	0
Abdominal pain upper	4	3	3	3	0	0
Headache	4	3	3	3	2	4
Abdominal pain	3	2	2	2	1	2
Nausea	2	2	7	6	4	7
Rash	2	2	7	6	1	2

In an assessment of adverse events by actual dose of deferasirox, headache, diarrhea and abdominal pain occurred more frequently at the higher doses. Additionally, all instances of blood creatinine increased, gastroenteritis, insomnia and fatigue occurred in subjects taking deferasirox at 10 or 20 mg/kg. These results suggest that to minimize the risk of adverse events, the lowest therapeutic dose of deferasirox should be used

Twenty-four subjects achieved an LIC <3 mg Fe/g dw after start of treatment. The only suspected AEs that occurred in this population with an incidence ≥5% more than in those not achieving an LIC <3 mg Fe/g dw were nausea (13% vs 4%) and abdominal pain upper (8% vs 3%). Thus, targeting an LIC <3 mg Fe/g d to stop treatment appears to be safe.

Overall, the safety profile of deferasirox in the NTDT subjects was similar to that seen in patients with thalassemia major and thus require the same warnings and precautions for use. No

new adverse events were identified. The analysis was limited by the short follow-up at any given dose.

Special Populations: An LIC <5 mg Fe/g dw was achieved by 7 of 16 (44%) children with NTDT treated with deferasirox, similar to the success rate in adults. There was no evidence for an increased rate of adverse events in children as compared to adults. Additionally, the rate of increase in creatinine in children was less than in adults. There are no data on the impact of treatment on growth and development in children with NTDT.

Diagnostics: The validation data for the use of R2 MRI confirmed its accuracy and reproducibility within the range of LIC of 3 - 30 mg Fe/g dw with a 10% error. The qualification data for the use of serum ferritin as a surrogate to identify an LIC <3 by R2 MRI showed that serum ferritin <300 ng/mL had a 97% sensitivity and a 44% specificity.

Overall Benefit-Risk Assessment: The results of Study A2209 indicate that one year of treatment with deferasirox at a starting dose of 10 mg/kg/day is sufficient to reduce the LIC to <5 mg Fe/g dw for a substantial proportion of patients with a baseline LIC 5-15 mg Fe/g dw, and that two years of treatment with a starting dose of 20 mg/kg/day would be similarly successful for those with higher baseline LICs. On the basis of a retrospective cross-sectional cohort study, achieving an LIC <5 mg Fe/g dw is reasonably likely to predict a reduced risk of serious iron-related complications. When LIC as measured by R2 MRI, a validated surrogate measure of iron burden, is used to select patients for therapy and guide dosing, the safety profile is acceptable. Safety is further assured by instructions for monitoring for early organ toxicities that require dose modification. It is the opinion of this reviewer that with appropriate labeling, the potential benefits of deferasirox for treatment of NTDT outweigh the risks.

1.3 Recommendations for Labeling

The following are recommendations specific for labeling for the NTDT population:

- Limit the indication to patients with NTDT who are at least 10 years of age and have an LIC ≥5 mg Fe/g dw.
- Indicate that the starting dose of deferasirox will be 10 mg/kg/day when the initial LIC is ≤15 mg Fe/g dw and 20 mg/kg/day when the initial LIC is >15 mg Fe/g dw.
- Indicate that a liver biopsy or an FDA-cleared or approved measure of LIC should be used to identify patients for treatment and to determine when the deferasirox dose should be modified or interrupted for efficacy.
- Recommend measurement of LIC at least every six months to assess efficacy.
- Recommend measurement of serum ferritin as a screening tool to monitor for overchelation.
- Interrupt treatment when the LIC is <3 mg Fe/g dw.

1.4 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.5 Recommendations for Postmarket Requirements and Commitments

PMR 1: Assess the long term safety of Exjade in patients with NTDT by conducting a trial of Exjade for the treatment of iron overload (LIC ≥5 mg Fe/g dw) in non-transfusion dependent thalassemia (NTDT) with 5 years total follow-up

PMR 2: Conduct a trial to assess the long term efficacy of Exjade in patients with NTDT and high LIC. The trial should assess response rates in the subset of patients with baseline LIC values >15 mg Fe/g dw (proportion of patients achieving an LIC <5 mg Fe/g dw and time to achieving an LIC <5 mg Fe/g dw). Five year follow-up of all subjects is necessary.

PMR 3: Assess the long term efficacy (and safety) of Exjade treatment to a target LIC of 3 mg Fe/g dw followed by one or more treatment holidays until the LIC is ≥5 mg Fe/g dw in patients with NTDT. Five year follow-up of all subjects is required.

PMR 4: Establish a registry of children (aged 10 to <17 years old at enrollment) with NTDT and an LIC ≥5 mg Fe/g dw treated with deferasirox and follow at least 40 children for up to 5 years to assess the long-term safety of treatment with deferasirox, including an assessment of growth with a comparison to children on a regular transfusion program receiving deferasirox. Provide annual reports on the enrollment and outcomes.

PMR 5: Complete a prospective, randomized trial in at least 150 patients with myelodysplastic syndromes (MDS) receiving Exjade to evaluate efficacy and safety of Exjade in this population. Subjects should be followed for a minimum of 3 years.

2 Introduction and Regulatory Background

2.1 Product Information

Drug Established Name: Deferasirox

Proposed Trade Name: Exjade®

Pharmacological Class: Tridentate iron chelator

Dosage Forms: Tablet for Oral Suspension - 125 mg, 250 mg, 500 mg

Proposed Indication: For the treatment of chronic iron overload in patients with non-transfusion-dependent thalassemia syndromes [redacted] aged 10 years and older.

Chelation therapy should only be initiated when there is evidence of iron overload (Liver Iron Concentration (LIC) ≥5 mg Fe/g dw or serum ferritin consistently > [redacted] microgram/L). [redacted]

Proposed Dose-Schedule: The recommended initial dose of Exjade is 10 mg/kg/day.

- The tablet is dispersed for ingestion by stirring in an appropriate amount of water, orange juice, or apple juice.
- [redacted] 6 months of treatment, consider a dose increase in increments of 5 to 10 mg/kg if the patient's LIC is >7 mg Fe/g dw, [redacted]
- Doses above 20 mg/kg are not recommended because there is no experience with doses above this level in patients with non-transfusion-dependent thalassemia syndromes.
- [redacted]
- For patients in whom the dose was increased to >10 mg/kg, dose reduction is recommended to 10 mg/kg or less when LIC is ≤7 mg Fe/g dw [redacted]
- Once a satisfactory body iron level has been achieved (LIC <3 mg Fe/g dw [redacted] treatment should be interrupted. Treatment should be re-initiated when there is evidence from clinical monitoring that chronic iron overload is present.

Exjade was approved on November 2, 2005 under subpart H for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. Chronic iron overload is described in labeling as the transfusion of approximately 100 mL/kg of packed red blood cells (approximately 20 units for a 40-kg patient) and a serum ferritin consistently >1000 mcg/L. The recommended initial daily dose of Exjade for this indication is 20 mg/kg body weight with increases in dose in steps of 5 or 10 mg/kg every 3-6 months up to a maximum of 40 mg/kg according to the individual patient's response and therapeutic goals. Therapy is to be interrupted if the serum ferritin is consistently below 500 mcg/L. Adequate and well-controlled studies to confirm clinical benefit have not yet been completed.

Since the initial approval of Exjade in 2005, there have been eight labeling revisions, seven of which affected safety or drug interaction information. Use of the drug is contraindicated for patients with a creatinine clearance <40 mL/min, poor performance status and high-risk myelodysplastic syndrome, platelet count <50 $x10^9$/L, or a known hypersensitivity to Exjade. The current version of the prescribing information carries a boxed warning regarding the risks of renal impairment, hepatic impairment, and gastrointestinal hemorrhage. Abdominal pain, nausea, vomiting, diarrhea, skin rashes, and increases in serum creatinine were the most frequent (>5%) adverse reactions reported with a suspected relationship to Exjade in study subjects treated for chronic iron overload. Gastrointestinal symptoms, increases in serum creatinine, and skin rash were dose-related. Auditory and ophthalmic testing annually is recommended during treatment with Exjade.

2.2 Currently Available Treatments for Proposed Indication

There are no approved treatments for the proposed indication of non-transfusion-dependent thalassemia (NTDT) syndromes. There are three iron chelators approved for treatment of chronic iron overload:

- Desferal® (deferoxamine mesylate) was approved in 1968 for the treatment of acute iron intoxication and of chronic iron overload due to transfusion-dependent anemias. Generic formulations are also marketed. Deferoxamine is available only for parenteral administration.
- Exjade® (deferasirox) was granted accelerated approval in 2005 for the treatment of chronic iron overload due to blood transfusions based on a reduction in biopsy-proven liver iron concentration by ≥3 mg Fe/g dry weight or to <7 mg Fe/g dry weight over 48 weeks, depending on the starting value. This was supported by a reduction in serum ferritin.
- Ferriprox® (deferiprone) was granted accelerated approval in 2011 for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. Approval was based on a ≥20% decline in serum ferritin levels in one year.

Published case series of NTDT patients treated with these chelators have reported a decrease in iron burden as measured by iron excretion, liver biopsy, serum ferritin and/or MRI (Cossu, Toccafondi et al, 1981; Pippard, Weatherall, 1988; Pootrakul, Sirankapracha et al, 2003; Voskaridou, Plata et al, 2010; Ladis, Berdousi et al, 2010; Akrawinthawong, Chaowalit et al, 2011).

2.3 Availability of Proposed Active Ingredient in the United States

Deferasirox is marketed in the United States only as Exjade.

2.4 Important Issues with Consideration to Related Drugs

The approved iron chelators are not related structurally, and each has a distinct safety profile. Class-specific toxicities would likely reflect the chelation effects of the drugs. Chelators not selective for Fe(III) may also induce adverse events related to loss of other minerals via chelation (De Virgilis, Congia et al, 1988a; Kushner, Porter, et al 2001; Kontoghiorghes, Kolnagou, et al 2010). The experience in the class suggests that overchelation or cross chelation may be related to both the dose of drug and individual iron load. For example, De Virgilis et al reported that initiation of high dose deferoxamine was associated with growth inhibition in patients with thalassemia major only when administration was started at the same time as transfusional therapy rather than after iron overload was established (De Virgilis, Congia, et al 1988b). Similarly, Porter et al reported that serum ferritin <2000 mcg/L was a risk factor for ototoxicity in patients with thalassemia treated with deferoxamine for transfusional hemosiderosis, especially high doses of deferoxamine (Porter, Jaswon, et al, 1989). They suggested that the dose of the iron chelator be tailored to the individual iron load in order to avoid toxicity.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Protocol CICL670A2209 (Study A2209) was submitted to IND 058554 on 3/6/2008. There was no End-of-Phase-2 meeting to discuss the design of the protocol prior to its submission. FDA comments to the applicant on 6/10/2008 noted that Study A2209 was not designed to assess the impact of treatment with deferasirox on survival or on an important morbidity for the patient population.

A pre-sNDA meeting was held 10/3/2011. FDA noted at that time that the proposed indication was broader than the study population, that long-term follow-up (years) would be desirable to assess safety and the risk benefit ratio in this population, and that the endpoint of change in liver iron concentration as assessed by MRI is an endpoint indicative of clinical benefit, but that the application should include data to demonstration the validation of the MRI endpoint.

2.6 Other Relevant Background Information

The non-transfusion-dependent thalassemias (NTDT) are defined as those which require limited or no transfusions for survival (Weatherall DJ, 2012). These include 30-60% of patients with β-thalassemia intermedia (TI), Hgb E-β-thalassemia, Hgb H disease, Hgb S-β-thalassemia, and Hgb C thalassemia. The clinical course of the NTDT population is highly variable but not well-characterized. Taher et al described the results of a cross sectional study on complications in patients with treatment-naive TI (Taher AT, Musallam KM, et al 2010a). Additional unpublished analyses of this dataset were provided in the submission by the applicant. They report that, despite being transfusion-independent, over half of the patients had a serious disease-related morbidity, and nearly a quarter had more than one complication (Table 4).

Table 4: Cross Sectional Analysis of Complication Rates Among Untreated TI Patients*

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Figure 1: Cross Sectional Analysis of Serum Ferritin by Age Among Untreated TI Patients*

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Age (years)

* N=120. From Taher AT, Musallam KM, et al 2010a

Hypogonadism, abnormal liver enzymes, hypothyroidism, and diabetes mellitus occurred in 4-15% of the treatment-naive TI patients (Table 4). These complications are known to result from iron overload. In NTDT, hepcidin levels are reduced by growth differentiation factor 15 from the expanded erythropoietic turnover and by hypoxia-inducible transcription factor (HIF) stimulated by the chronic anemia; HIF also upregulates ferroportin production (Origa, Galanello et al, 2007). These changes result in increased absorption of iron from the gastrointestinal tract and mobilization of iron from the reticuloendothelial system, with subsequent deposition in the liver and other tissues. Thus, even in the absence of transfusions, iron overload may occur in NTDT patients, including those as young as 5 years of age (Cossu, Toccafondi et al, 1981). Although the level of iron burden as assessed by serum ferritin may increase with age in patients with TI (Figure 1), such a relationship has not been confirmed for all types of NTDT (Pakbaz, Fischer, et al, 2007; Lal, Goldrich, et al, 2011).

The place of chelation therapy in the management of NTDT appears to be evolving in response to emerging information about the natural history of the disease. In the OPTIMAL CARE study, a multicenter, cross-sectional cohort study, patients with TI who were not transfused but received chelation therapy had a lower mean complication rate than those who were neither transfused nor chelated (Table 5) (Taher, Musallam, et al, 2010b). Musallam et al further identified an LIC $\geq$6 mg Fe/g dw as the best cut-point to identify patients with endocrine and bone abnormalities (Figure 2) (Musallam, Cappellini, et al, 2011). On the basis of these retrospective analyses, the Thalassaemia International Federation now recommends that NTDT patients be monitored at least annually for iron burden and receive chelation therapy when the LIC is >5 mg Fe/g dw (Thalassaemia International Federation, 2012). The complication rate appears even lower with the combination of chelation and transfusions than with chelation alone in patients with TI (Table 5), but how to incorporate an on-going transfusion program into therapy of asymptomatic TI patients is not yet clear.

Table 5: The OPTIMAL CARE Study: Complication Rates in TI Patients by Treatment History

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Taher, Musallam, et al, 2010b
*Mean number of complications per patient

Figure 2: Cross Sectional Analysis of Bone and Endocrine Complications by Age and LIC Among Untreated TI Patients

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Adapted from Musallam, Cappellini, et al, 2011

2.7 Compliance with the Pediatric Research Equity Act

A partial waiver of pediatric studies in patients with NTDT less than 10 years of age was granted as studies were considered impracticable.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

NDA 021882 Efficacy Supplement 015 was received 12/23/2012 as an electronic submission organized in CTD format. The submission was found to be complete and was filed 2/21/2012. A major amendment was submitted 8/6/2012. Additional amendments are listed in Table 6.

Table 6: NDA 021882 S-015 Submission and Amendments

SDN	Received	Category	Subcategory
678	12/23/2011	Original	Original Submission
695	02/13/2012	Correspondence	Establishment Information
704	03/13/2012	Biometrics	Response To Information Request
713	04/18/2012	Clinical	Safety Update - 120-Day Safety Update
716	05/07/2012	Clinical	Response To Information Request
718	05/30/2012	Clinical	Response To Information Request
721	07/13/2012	Correspondence	Revised financial disclosures
723	08/06/2012	Clinical	Efficacy Update - 120-Day Efficacy Update
724	08/13/2012	Clinical	Response To Information Request
732	09/25/2012	Clinical	Response To Information Request
733	09/26/2012	Labeling	Prescribing Information Draft
736	10/03/2012	Clinical	Response To Information Request
739	10/09/2012	Clinical	Response To Information Request
752	10/31/2012	Clinical	Response To Information Request
753	10/31/2012	Clinical	Response To Information Request
758	11/13/2012	Clinical	Response To Information Request
759	11/19/2012	Clinical	Response To Information Request
765	11/29/2012	Clinical	Response To Information Request
766	11/30/2012	Clinical	Clinical Study Report – Extension Protocol
767	12/05/2012	Clinical	Extension Protocol Datasets
770	12/07/2012	Clinical	PMR Proposals

3.2 Compliance with Good Clinical Practices

The applicant stated that all studies in the deferasirox clinical development program were conducted in full compliance with Good Clinical Practice (GCP). All studies were monitored by Novartis personnel or a contract organization for compliance to the protocol and its procedures. Two sites for Study A2209 were audited by the applicant (Sites 1652 and 1653), and these both demonstrated compliance with GCP. An additional quality assessment was performed at Site 1831 in June, 2010. This assessment showed incomplete adherence to protocol conduct, protocol deviation reporting, informed consent process, serious adverse event reporting, data management and source document reporting, and drug accountability. A corrective action plan was instituted, and the applicant reported that it was completed successfully in October 2010.

The applicant also provided an assessment of protocol deviations across the clinical sites for Study A2209. A protocol deviation for reported for 106 (64%) of the subjects, and the deviation was significant enough to exclude 36 (22%) of the subjects from the per protocol analysis. The

number of subjects with protocol deviations did not differ significantly across the treatment arms of the study (see Section 6.1.4), so no concern was raised over bias due to an imbalance in deviations between study arms.

The Division of Scientific Investigations conducted inspections at the clinical sites for Study A2209 in Bangkok, Thailand (Site 1652) and Cagliari, Italy (Site 0404). These sites were chosen on the basis of the number of subjects treated. There were no significant issues in data integrity identified at either site that affected the safety or efficacy analyses.

3.3 Financial Disclosures

The applicant obtained financial disclosure forms from all of the clinical investigators that participated in Study A2209. None of the clinical investigators were full or part-time employees of Novartis Pharmaceuticals Corporation. Three clinical investigators (Drs. (b) (6) (Site (b) (6)), (b) (6) (Site (b) (6)) and (b) (6) (Site (b) (6)) had financial arrangements and interests that required disclosure and certification. The clinical sites for these three investigators account for 27% of the randomized subjects. To ensure there was no bias associated with these financial conflicts of interest, exploratory analyses were performed for subject exclusion, demographics and results of the primary endpoint comparing these three sites with the rest of the study population (Section 6.1.10.2).

4 Significant Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There is no new information regarding manufacturing in this supplement.

4.2 Clinical Microbiology

There is no new information regarding drug substance in this supplement.

4.3 Preclinical Pharmacology/Toxicology

There is no new nonclinical information submitted in this supplement.

4.4 Clinical Pharmacology

There were no significant issues identified by the Clinical Pharmacology reviewer.

4.5 Pharmacovigilance

The Office of Surveillance and Epidemiology reviewed the pharmacovigilance plan submitted 4/20/2102. They recommended enhanced pharmacovigilance for serious or severe reports of liver toxicity, renal toxicity and all fatal outcomes.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 7. Deferasirox Clinical Trials

Trials / Status	Design	Population	Primary Endpoint
A2209 Core (THALASSA) Completed	Phase II, randomized, double-blind, placebo-controlled, four-arm trial ·Deferasirox 5 mg/kg/day ·Deferasirox 10 mg/kg/day ·Placebo for 5 mg/kg/day ·Placebo for 10 mg/kg/day	Thalassemia intermedia at least 10 years of age who had a LIC ≥ 5 mg Fe/g dw by R2 MRI and had not been transfused for ≥6 months 166 subjects randomized (17 <17 years of age)	Change in MRI-measured LIC from baseline to 12 months
A2209 Extension On-going	Phase II, open-label trial ·Responders with an LIC >3 mg Fe/g dw continue on current deferasirox dose to maximum based on LIC ·Nonresponders with an LIC 3-15 mg Fe/g dw receive 10 mg/kg/day · Nonresponders with an LIC >15 mg Fe/g dw receive 20 mg/kg/day	Thalassemia intermedia subjects who completed A2209 Core without renal or hepatic toxicity and were not on a regular transfusion program 132 subjects enrolled (14 <17 years of age)	Proportion of subjects who achieve an LIC < 5 mg Fe/g dw at any time from start of treatment
A2202 Core Completed	Phase I/II open label, dose escalation trial ·Deferasirox 5 mg/kg/day ·Deferasirox 10 mg/kg/day ·Deferasirox 15 mg/kg/day ·Deferasirox 20 mg/kg/day	Hereditary hemochromatosis at least 18 years of age with ferritin 300-2000 mcg/L and transferrin saturation ≥ 45%. 49 subjects enrolled (None <17 years of age)	(Results used only for assessment of safety)
A2202 Extension Completed	Phase II, open-label trial ·Continue on deferasirox dose assigned in the Core trial	Hereditary hemochromatosis subjects who completed A2202 Core without toxicity 26 subjects enrolled (None <17 years of age)	(Results used only for assessment of safety)

5.2 Review Strategy

The key materials used for the review of efficacy and safety include:

- NDA 021882 Supplement 15
- Relevant published literature
- Relevant information in the public domain

Listing datasets MLRSSCRF and MMRISCRF, and analysis datasets SCRNPATS, ACND, ACOM, ACPL, AHIS, AHIS2, ARND, ASPN, ATMT, LRSGRD and NOVIOPTO were included in the original submission but not in the 120-day safety update (A.713) or the 120-day

efficacy update (A.723). When information from such datasets was needed, the version in the original submission was used. Otherwise, the datasets used in the analyses were generally those submitted in the 120-day safety or efficacy updates, specifically the listing datasets. The listing datasets included all raw data available, while the analysis datasets in the 120-day updates were limited to information dated through 12/1/2011, excluding information with later dates. Since this reviewer used the raw datasets for analyses, while the applicant used the analysis datasets, there were minor differences between the applicant's reports and the results of similar analyses in this review.

The results from the A2209 Core and Extension protocols were used for the analysis of efficacy. A discussion of the basis for use of achieving an LIC <5 mg Fe/g dw as the endpoint for efficacy is provided in Section 6.1.5.2. Wherever possible, the endpoints were assessed in each protocol separately in an attempt to determine reproducibility of the effect. Results from the literature review were also considered.

The results from both A2209 and A2202 were used in the analysis of safety. Since the patient populations were clearly not interchangeable, the safety profiles were developed separately for A2209 and A2202. In addition, within each study, the safety data from the Core and Extension protocols were pooled to allow for an analysis of changes in toxicity over time.

The Extension protocol was on-going at the time of submission of the 120-day update, and it is acknowledged that the dataset used was therefore incomplete. The incompleteness of the outcomes and safety data was taken into account wherever possible in the initial analysis of the study. The final clinical study report and datasets for the Extension protocol was submitted in A.767 and A.770 after the review was drafted. This new information was used only for the analyses presented in Sections 6.1.12 and 7.7.3, addenda to the main review.

Analyses by the clinical reviewer were performed largely using JMP 9.0 (SAS Institute, Inc, Cary, NC). MedCalc 12.3.0 (MedCalc Software, Mariakerke, Belgium) was used for qualification of ferritin levels as surrogates for specific LICs. MedDRA Adverse Events Diagnostic (MAED) 1.0 (Clinical Trials & Surveys Corporation, Owings Mills, MD) was used to assess for safety signals.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study A2209

Study A2209 included a Core protocol and an Extension protocol for treatment of patients with NTDT. The Core protocol was designed as a randomized, Phase 2 placebo-controlled trial to assess two different doses of deferasirox over a 12 month period of time. The primary objective of the Core protocol was to assess the comparative efficacy of deferasirox at starting doses of 5 or 10 mg/kg/day. The secondary objectives were to compare the efficacy after 6 months of treatment, to compare change in serum ferritin over one year of treatment, to evaluate the safety of both regimens of deferasirox versus placebo, 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 parameters, and to evaluate the iron accumulation rate in the subjects treated with placebo.

The accrual target was 156 subjects (52 in each deferasirox arm and 26 in each placebo arm). The assumptions for the sample size calculation included an expected mean decrease of 3 mg Fe/g dw in LIC from baseline to week 52 with a standard deviation of 4 mg Fe/g dw and an expected drop-out rate of 10%. A blinded sample size reassessment using the week 24 data was used to confirm the study design.

Subjects who completed the Core protocol could be consented and enrolled on the Extension protocol. The Extension protocol was an open-label trial to gain additional information about the effects of treatment with deferasirox. The protocol duration was 12 months. Those subjects who were on the treatment arms in the Core protocol continued treatment with open-label deferasirox (final total duration of treatment was 24 months). Those who were on the placebo arms in the Core protocol were started on active drug in the Extension protocol (final total duration of active treatment was 12 months).

The primary objectives of the Extension protocol were to evaluate the number of patients reaching an LIC < 5 mg Fe/g dw and to evaluate the long-term safety of deferasirox administration in patients with NTDT. The secondary objectives were to evaluate change in serum ferritin from baseline in patients treated with deferasirox, to evaluate the relationship between serum ferritin and LIC, to evaluate the change from baseline in hematological and iron metabolism parameters, and to evaluate the rate of iron accumulation based on LIC assessment in patients who stopped the therapy during the study

Key eligibility criteria for the A2209 Core protocol:

- Male or female age ≥ 10 years with NTDT other than Hgb S variants
- No transfusion within 6 months prior to entry into the study
- Weight of at least 20 kg to allow for dosing restricted by tablet size
- LIC≥ 5 mg Fe/g dw measured by R2 MRI at screening
- Serum ferritin > 300 ng/mL at screening
- Not anticipated to require regular transfusions during the study.
- No chelation therapy within 1 month prior to study start
- No prior use of deferasirox
- No significant proteinuria (defined as a urine protein/urine creatinine ratio > 1.0
- Serum creatinine within normal limits and creatinine clearance >60 ml/min
- ALT ≤5x ULN and no evidence of cirrhosis
- No active hepatitis B or C, or HIV
- No concomitant therapy with hydroxyurea, erythropoietin, butyrate
- No history of clinically relevant ocular and/or auditory toxicity due to chelation therapy

Key eligibility criteria for the A2209 Extension protocol:

- Completed the A2209 Core protocol

• No renal toxicity (defined as a continuous increase in serum creatinine ≥ 33% above the baseline value or a serum creatinine greater than ULN who did not improve after drug interruption or dose reduction in the core study)
• No hepatic toxicity (defined as a continuous increase in ALT greater than 2 times the baseline value and > 5x ULN who did not improve after drug interruption or dose reduction in the core study)
• No evidence of progressive proteinuria
• No clinical need for regular transfusions

Key elements of the Study A2209 treatment plan and efficacy assessments:

Study A2209 Core Protocol

Baseline *MRI** *Ferritin*			**Blinded Treatment Weeks 1-24** *Ferritin monthly*[1]		**Week 24** *MRI* *Ferritin*[1]		**Blinded Treatment Weeks 25-52** *Ferritin monthly*[1]	**Month 12 Week 52** *MRI* *Ferritin*
LIC ≥ 5 and serum ferritin > 300 ng/mL	**Randomize**	2 →	Deferasirox 5 mg/kg/day	**Reassess**	LIC <7 or response[2] ≥15%	→	Continue assigned dose	**End of Core Protocol**
		1 →	Placebo 5 mg/kg/day					
		2 →	Deferasirox 10 mg/kg/day		LIC ≥7 and response[2] <15%	→	Double assigned dose	
		1 →	Placebo 10 mg/kg/day					

*LIC was determined using R2 MRI data assessed by FerriScan at a central facility.
[1]Hold dose for serum ferritin <100 ng/mL and reassess LIC by MRI. Resume when the LIC is ≥ 5 and serum ferritin > 300 ng/mL
[2]Defined as decrease in LIC from Core protocol baseline to Week 24

Study A2209 Extension Protocol

Month 12 *MRI** *Ferritin*			**Open Label Treatment Months 12-18** *Ferritin monthly*[2]		**Month 18** *MRI* *Ferritin*[2]		**Open Label Treatment Months 18-24** *Ferritin monthly*[2]	**Month 24** *MRI* *Ferritin*
Core Protocol Responder[1]	LIC <3	→	Interrupt[3]	**Reassess**	LIC <3	→	Interrupt[3]	**End of Extension Protocol**
	LIC 3-15	→	Continue Core dose up to 10 mg/kg/day		LIC 3-7	→	Continue up to 10 mg/kg/day	
	LIC >15	→	Continue Core dose up to 20 mg/kg/day		LIC >7 and response ≥15%	→	No change	
Not a Core Protocol Responder[1]	LIC <3	→	Interrupt[3]					
	LIC 3-15	→	10 mg/kg/day		LIC >7 and response <15%	→	Double dose up to 20 mg/kg/day	
	LIC >15	→	20 mg/kg/day					

*LIC was determined using R2 MRI data assessed by FerriScan at a central facility.
[1]Defined as decrease in LIC by >30% from Core protocol baseline to Week 52
[2]Hold dose for serum ferritin <100 ng/mL and reassess LIC by MRI. Resume when the LIC is ≥ 5.
[3]Hold dose until LIC >5 on subsequent monitoring MRI

Key elements of the A2209 safety assessments

In both the Core and Extension protocols, patients were seen at least monthly to assess adverse reactions, vital signs, physical examination, hematology, biochemistry, urinalysis, and iron metabolism parameters. The visit at month 12 in the Core protocol and at month 24 in the Extension protocol included ECG, echocardiography, ocular and auditory examinations.

Key efficacy analyses in the A2209 Core protocol

The primary endpoint of the Core protocol was the absolute change in LIC from baseline to week 52 by treatment arm. The analysis population was all randomized subjects, and the placebo arms were pooled. For those missing the LIC at week 52, the last observation was carried forward, and those with no post-baseline LIC were excluded from the analysis. The endpoint was evaluated by using a one-way linear model with treatment group as a factor with 3 levels. Analysis of variance (ANOVA) was performed with the family-wise type I error rate was set to 0.025. The absolute change in LIC at week 52 from the two deferasirox groups was compared by using a two-sided t-test at 5% alpha level.

Supporting analyses included descriptive statistics for the absolute change in LIC from baseline to week 24, week 52 and for last available LIC measurement, the number of patients with at least 30% reduction in LIC at the end of study, and the number of patients with LIC $\leq$ 7 mg Fe/g dw at the end of study. Logistic regression was used to assess the proportion of patients with a LIC decrease by at least 3 mg Fe/g dw at the end of study. The primary endpoint was also assessed by analysis of covariance (ANCOVA) using baseline LIC with and without demographic factors as covariates.

Analysis of the secondary endpoints included ANOVA to assess change in LIC from baseline to week 24 by treatment arm, one-sided t-tests using Dunnett's adjustment to compare the change in average ferritin from baseline to fourth quarter, description of the change in LIC by whether the dose was doubled at week 24, and description by quarter for the hematological parameters and iron metabolism parameters.

Key efficacy analyses in the A2209 Extension protocol: The primary endpoint of the Extension protocol was the proportion of subjects who achieved an LIC <5 mg Fe/g dw. The analysis population was all subjects enrolled on the Extension protocol; those with no post-baseline LIC measurement were scored as failures. A secondary analysis of the primary endpoint was conducted by arm in the Core protocol. Secondary endpoints assessed by quarter included the absolute change in serum ferritin, hematological parameters and iron metabolism parameters.

Additional analyses for both protocol included regression analysis to assess the correlation between serum ferritin and LIC, and for subjects who stopped treatment, and descriptive statistics for change in LIC from therapy stop for each following 6 month visit and for last available LIC measurement.

Key revisions to Study A2209: There were three amendments to Study A2209. The following amendments were considered major:

Amendment 2: 8/14/2009	Added a provision for rescreening screening failures; increased the maximum ALT for eligibility to 5x ULN; deleted the maximum lifetime transfusions of 20 units for eligibility; added LIC assessment at week 24; added secondary objectives to assess LIC change at week 24, to assess the effect of dose doubling at week 24; to determine the proportion of subjects with an LIC decrease >3; 30% reduction in LIC or LIC ≤7 at end of study; added a dose increase at week 24 for elevated LIC without response; revised dose modifications for gastrointestinal or renal toxicity and skin rash; increased the threshold for stopping treatment from an LIC <2 to an LIC<3; and added an analysis of iron accumulation in the placebo arms as well as additional analyses to address the new secondary objectives.
Amendment 3: 10/13/2009	Added the Extension protocol

5.3.2 Study A2202

Study A2209 included a Core protocol and an Extension protocol for treatment of patients with hereditary hemochromatosis. The Core protocol was designed as a Phase 1/2 open-label, dose-escalation trial to assess four different doses of deferasirox (5-20 mg/kg/day) over a 6 month period of time. The accrual target was 40 subjects, including at least 8 evaluable subjects at each dose level and up to 16 evaluable subjects at the Phase 2 dose. The primary objective was to assess safety. Secondary objectives were to assess the effect of treatment on serum ferritin and characterize of the pharmacokinetics of deferasirox.

Subjects who completed the Core protocol could be consented and enrolled on the Extension protocol. The Extension protocol was an open-label trial to gain additional information about the effects of treatment with deferasirox. The protocol duration was 6 months (final total duration of treatment was 12 months).

Key eligibility criteria for the A2202 Core protocol:
- Male or female age ≥ 18 years homozygous for the C282Y mutation
- No transfusion within 6 months prior to entry into the study
- Hgb <13 mg/dL for males and >12 mg/dL for females
- Serum ferritin 300-2000 ng/mL and transferrin saturation ≥45%
- No phlebotomy within 2 weeks of the screening visit
- No deferoxamine within 1 month prior to study start
- No prior use of deferasirox or deferiprone
- Serum creatinine within normal limits
- ALT ≤2x ULN and no evidence of cirrhosis
- No active hepatitis B or C, or HIV
- No history of clinically relevant ocular and/or auditory toxicity due to chelation therapy

Key eligibility criteria for the A2202 Extension protocol:
- Completed the A2209 Core protocol
- No unacceptable toxicity

Key elements of the Study A2202 treatment plan:

The subjects were treated with the assigned dose of deferasirox (5, 10 or 15 mg/kg/day) for 24 weeks on the Core protocol. (The 20 mg/kg/day cohort was not pursued upon recommendation of the Independent Safety Monitoring Committee when the dose of 15 mg/kg/day was found to adequately reduce the ferritin levels.) Study drug was held when the ferritin was <100 ng/mL and restarted when >300 ng/mL.

In the Extension protocol, the subjects continued on the dose assigned in the Core protocol. The dose of deferasirox could be increased to the highest open dose level in the Core protocol if the serum ferritin was >300 ng/mL and there was <10% decrease in ferritin over 2 months or the ferritin increased above baseline on 2 consecutive visits. Study drug was held when the ferritin was <100 ng/mL and restarted when >300 ng/mL.

Key elements of the A2202 safety assessments:

Patients were seen biweekly in the Core protocol and monthly in the Extension protocol to assess adverse reactions, vital signs, physical examination, hematology, biochemistry, iron metabolism parameters, and serum ferritin. Urinalysis was performed every 12 weeks in the Core protocol and monthly in the Extension protocol. The visit at week 24 in the Core protocol and at month 12 in the Extension protocol included ECG, ocular examination and auditory testing.

Major revisions to Study A2202: There were four amendments to Study A2202. The following amendments were considered major:

Amendment 2: 12/21/2006	Reduced the minimum Hgb for eligibility for males to 13 gm/dL, reduced the maximum ALT for eligibility to twice the ULN, revised dose modifications for ALT and serum creatinine, and added monitoring for proteinuria,
Amendment 3: 5/1/2007	Increased the maximum ferritin for eligibility to 2000 ng/mL, increased the minimum accrual per cohort from 6 to 8 subjects, and added the option to increase the dose upon enrollment to the Extension protocol.

6 Review of Efficacy

Efficacy Summary

The clinical development program consists of Study A2209 which included two protocols for treatment of patients with NTDT over the age of 10 years with an LIC ≥5 mg Fe/g dw by R2 MRI. The Core protocol was a blinded, randomized trial of one year duration that compared two dose levels of deferasirox (5 mg/kg/day and 10 mg/kg/day) and placebo; after six months of therapy, the dose could be doubled if there was no response. The Extension protocol was an open-label, single-arm trial of one year duration for subjects treated on the Core protocol (including cross-over of subjects from the placebo arm). Treatment in the Extension protocol was assigned to largely 10 mg/kg/day or 20 mg/kg/day depending on the LIC at enrollment, and after six months of therapy, the dose could be increased if the LIC was >7 and there was no response.

The Core protocol accrued 166 subjects, including 17 children. The Extension protocol accrued 133 of the subjects from the Core protocol; however, only 130 were treated, including 48 who crossed over from the placebo arm in the Core protocol. Achieving an LIC <5 mg Fe/g dw was considered the endpoint reasonably likely to predict a clinical benefit. The absolute reduction in LIC was considered supportive. Missing data was substantial; 20 (13%) of the subjects were missing the LIC measurement at baseline or at week 52 in the Core protocol. The Extension protocol was on-going at the time of the analysis. The results of the analysis of the available data showed:

- Response was dose-dependent. In the Core protocol, the target LIC was achieved within one year by 15% with a starting deferasirox dose of 5 mg/kg/day, 27% with 10 mg/kg/day, and 4% with placebo.

- Achieving the target LIC also depended on baseline LIC. For those with a baseline LIC ≤15 treated with deferasirox 10 mg/kg/day, the target LIC was reached within one year by 41% in the Core protocol and 51% in the Extension protocol, but by only 20% of those treated with 5 mg/kg/day. For those with a baseline LIC > 15, 10% achieved the target LIC in one year when treated with a starting dose of 20 mg/kg/day, and 0-5% when treated with 10 mg/kg/day, and none at 5 mg/kg/day.

- The absolute reduction in LIC at one year was also dose-dependent, with means being -1.9 to -1.5 mg Fe/g dw for 5 mg/kg/day, -3.8 to -2.8 for 10 mg/kg/day, and -9.1 for 20 mg/kg/day. The magnitude of the reduction in LIC suggests that two years of therapy at 20 mg/kg/day would allow achievement of the target LIC for those with a baseline LIC >15.

- When corrected for deferasirox dose and baseline LIC, achievement of the target LIC was consistent in subgroup analyses across age, gender, race, thalassemia diagnosis, splenectomy, number of prior transfusions and prior chelation therapy.

- Only 24 (15%) of the 158 treated subjects achieved an LIC <3 and interrupted drug use.

- The efficacy results were supported by two published pilot studies of deferasirox for treatment of patients with NTDT.

- In the analysis of secondary endpoints of iron metabolism and erythropoiesis in the Core protocol, there was a significant dose-dependent reduction in ferritin and increase in transferrin, but there were no significant dose-dependent changes at one year in labile plasma iron, nontransferrin bound iron, erythropoietin, hepcidin, or growth differentiation factor 15.

- The validation data for the use of R2 MRI confirmed its accuracy and reproducibility. Within the range of LIC of 3 - 30 mg Fe/g dw, there was a 10% error.

- The qualification data for the use of serum ferritin as a surrogate to identify an LIC <3 by R2 MRI showed that serum ferritin <300 ng/mL had a 97% sensitivity and a 44% specificity.

Overall, the efficacy data support the use of deferasirox 10 mg/kg/day for treatment of patients with an LIC ≤15. There were too few subjects who reached an LIC <3 to confirm the proposed strategy for maintaining the target LIC once it is reached. Longer follow-up is need to confirm that 20 mg/kg/day will be effective for those with an LIC>15. R2 MRI, but not serum ferritin. is a valid alternative to liver biopsy to identify patients for treatment and to guide changes in dosing.

6.1 Indication

The proposed indication is for treatment of chronic iron overload in patients with NTDT who have an LIC ≥5 mg Fe/g dw or serum ferritin consistently >800 mcg/L.

6.1.1 Methods

The review strategy has been described in Section 5.2. See Section 5.3.1 for the design of Study A2209. In this disease, chronic iron overload may be due to gastrointestinal absorption with or without occasional transfusions. This new indication is to be distinguished from the current approved indication for which chronic iron overload is due to blood transfusions (defined as 100 mL/kg of packed red blood cells and a serum ferritin >1000 mcg/L) without regard to diagnosis.

6.1.2 Demographics

Three hundred thirty-nine subjects were screened at 28 clinical sites worldwide. Of these screened subjects, 173 (51%) failed to meet eligibility, and the other 166 (49%) proceeded to randomization. The reason for screening failure included an LIC or serum ferritin that was too low (54%), screening laboratory test abnormality (14%), subject withdrew consent (11%), recent transfusion or more than 20 transfusions lifetime (10%), unable, unwilling or unsuitable for screening or protocol procedures (7%), and ineligible by medical history and/or medication use (3%). Characteristics of all screened subjects are shown in Table 8. In comparison to the randomized population, the subjects who failed screening were significantly younger, had fewer

transfusions, and had a lower iron burden as measured by LIC or ferritin. Overall, although there was a high proportion of screening failures, there was no evidence that eligible subjects were excluded from randomization.

Table 8: Characteristics of All Screened Subjects

	All Screened Subjects (n=339)	Screen Failures (n=173) [1]	Randomized (n=166)	p [2]
Median Age (range)	29 (10 - 70) yrs	26 (10 - 70) yrs	32 (10 - 69) yrs	0.002
Age <17 years	57 (17%)	40 (23%)	17 (10%)	0.001
Gender Male	181 (53%)	92 (53%)	89 (54%)	0.94
Female	158 (47%)	81 (47%)	77 (46%)	
Race White	206 (61%)	112 (64%)	94 (57%)	0.01
Asian	129 (38%)	60 (35%)	69 (42%)	
Black	2 (<1%)	0	2 (1%)	
Other	2 (<1%)	1 (<1%)	1 (<1%)	
Diagnosis β-Thalassemia	200 (59%)	105 (64%)	95 (57%)	0.02
Hgb E β-Thalassemia	77 (23%)	28 (17%)	49 (30%)	
α-Thalassemia	52 (15%)	30 (18%)	22 (13)	
Other Thalassemia	2 (<1%)	2 (1%)	0	
Prior Splenectomy	185 (55%)	97 (58%)	88 (53%)	0.38
Prior Transfusions	267 (80%)	122 (73%)	145 (87%)	0.001
Prior Chelation Therapy	57 (27%)	13 (26%)	44 (27%)	0.91
Median LIC (range)	8.9 (0.7 - 49.1) mg/g dw	4.1 (0.7 - 41.5) mg/g dw	12.1 (2.6 - 49.1) mg/g dw	<0.001
Median Ferritin (range)	843 (24 - 6418) mcg/L	710 (24 - 5294) mcg/L	992 (304 - 6419) mcg/L	<0.001

[1] Demographic information was incomplete for the screen failures. The denominator for screen failures is 165 for diagnosis, 168 for prior splenectomy, 167 for transfusions, 50 for prior chelation therapy, 117 for LIC, and 169 for ferritin.
[2] Screen failures vs randomized

One hundred sixty-six subjects were randomized at 27 clinical sites. Only four (2%) of the subjects were treated in the US. The demographics and baseline measures of iron burden for the randomized subjects are shown in Table 9. There were no significant differences between arms in any of the characteristics presented except for prior chelation therapy; the deferasirox 5 mg/kg/day (D5) arm had the lowest proportion of subjects with prior chelation use (15%), and the placebo arm had the highest proportion (36%). Deferoxamine was the chelation agent used most frequently (7/8 subjects in arm D5, 15/16 subjects on deferasirox 10 mg/kg/day (arm D10), and 17/20 subjects on placebo). No randomized subjects had received deferasirox prior to screening.

It is noteworthy that 82-91% of the subjects had received prior transfusions. The median number of prior transfusions was 6-8 across the 3 protocol arms. Twenty-six patients (16%) had received 20 or more transfusions lifetime prior to randomization.

Table 9: Characteristics of Randomized Subjects by Treatment Arm

	Deferasirox 5 mg/kg/day (n=55)	Deferasirox 10 mg/kg/day (n=55)	Placebo (n=56)	p[1]
Median Age (range)	33 (10 - 60) yrs	31 (12-69) yrs	32 (10 - 59) yrs	0.69
Age <17 years	6 (11%)	6 (11%)	5 (9%)	0.92
Gender Male	29 (53%)	29 (53%)	31 (55%)	0.94
Female	26 (47%)	26 (47%)	25 (45%)	
Race White	31(56%)	30 (55%)	33 (59%)	0.67
Asian	23 (42%)	24 (44%)	22 (39%)	
Black	1 (2%)	1 (2%)	0	
Other	0	0	1 (2%)	
Diagnosis β-Thalassemia	32 (58%)	30 (55%)	33 (59%)	0.80
Hgb E β-Thalassemia	18 (33%)	16 (29%)	15 (27%)	
α-Thalassemia	5 (9%)	9 (16%)	8 (14%)	
Prior Splenectomy	29 (53%)	31 (56%)	28 (50%)	0.80
Prior Transfusions	49 (89%)	50 (91%)	46 (82%)	0.35
Median Number of Transfusions (range)	8 (1-43)	8 (1-52)	6 (1-75)	0.58
Prior Chelation Therapy	8 (15%)	16 (29%)	20 (36%)	0.04
Median LIC (range)	11.7 (2.6 - 38.6) mg/g dw	11.7 (5.0 - 32.8) mg/g dw	13.0 (5.0 - 49.1) mg/g dw	0.66
Median Ferritin (range)	988 (370- 5609) mcg/L	1015 (342 - 4224) mcg/L	994 (304 - 6419) mcg/L	0.78

[1] One-way analysis across treatment groups

6.1.3 Subject Disposition

The first subject was enrolled on the A2209 Core protocol 11/24/2008, and the last subject completed study procedures on 6/22/2011. The first subject was enrolled on the A2209 Extension protocol 2/19/2011, and the study was still on-going when the 120-day safety update was submitted.

The disposition of all randomized subjects is shown in Table 10. All subjects have completed or withdrawn from the Core protocol. One hundred thirty-three (80%) of the subjects from the Core protocol continued on the Extension protocol. Of these, 94 subjects completed the Extension protocol or withdrew early, and 39 were continuing treatment; however, 128 (97%) of the subjects on the Extension protocol had at least 18 months of follow-up recorded. It should also be noted that in the Extension protocol, 130 subjects were treated with open-label deferasirox, while three with low LICs were observed off therapy.

Table 10: Disposition of Randomized Subjects

	A2209 Core (n=166)	A2209 Extension (n=133)
Completed	148 (89%)	91 (69%)
On-going	0	39 (29%)
Discontinued	18 (11%)	3 (2%)
Discontinuation Reasons		
Adverse Event	6	2
Abnormal Test	1	0
Withdrew Consent	5	0
Lost Follow-up	4	1
Protocol Deviation	2	0

Table 11 provides the disposition of subjects by treatment arm in the Core protocol. There was no significant difference between the treatment arms in the completion rate or in the reasons for early discontinuation.

Table 11: Disposition of Subjects by Treatment Arm in Study A2209 Core Protocol

	Deferasirox 5 mg/kg/day (n=55)	Deferasirox 10 mg/kg/day (n=55)	Placebo (n=56)
Completed	48 (87%)	49 (89%)	51 (91%)
Discontinued	7 (13%)	6 (11%)	5 (9%)
Discontinuation Reasons			
Adverse Event	2	3	1
Abnormal Test	0	0	1
Withdrew Consent	1	2	2
Lost Follow-up	3	1	0
Protocol Deviation	1	0	1

6.1.4 Protocol Deviations

A total of 349 protocol deviations were reported for 115 subjects in Study A2209. These included 266 deviations in A2209 Core and 83 deviations in A2209 Extension. The most common deviations were missing laboratory testing, consent issues (arising largely from late reconsent after protocol amendments), errors in the dose administered, and one or more measurement of LIC by MRI after start of treatment. Table 12 lists the number of deviations by broad criterion for the Core and Extension protocols.

Table 12: Protocol Deviations

	A2209 Core (n=166)	A2209 Extension (n=132)
Subjects with Deviations	106 (64%)	40 (30%)
Deviations	266	83
Deviations by Criterion		
Consent Issue	31	0
Doses Missed	13	1
Dosing Error	31	56
Ineligible By History	2	0
Ineligible By Labs	6	0
LIC Baseline Missing	2	0
LIC Performed Late	2	1
LIC Post Missing	27	5
LIC None Done Post	6	2
SAE Report Late	4	1
Safety Test Late	9	0
Safety Test Missing	133	17

Table 13: Protocol Deviations by Treatment Arm in Study A2209 Core Protocol

	Deferasirox 5 mg/kg/day (n=55)	Deferasirox 10 mg/kg/day (n=55)	Placebo (n=56)
Subjects with Deviations	38 (69%)	35 (64%)	33 (59%)
Deviations	97	87	82
Deviations by Criterion			
Consent Issue	12	9	10
Doses Missed	6	4	3
Dosing Error	13	11	7
Ineligible By History	1	1	0
Ineligible By Labs	1	0	5
LIC Baseline Missing	1	0	1
LIC Performed Late	1	1	0
LIC Post Missing	6	15	6
LIC Not Done Post	4	1	1
SAE Report Late	1	2	1
Safety Test Late	2	1	6
Safety Test Missing	49	42	42
Subjects with Missing LIC at Baseline or at Week 52	7 (13%)	11 (20%)	2 (4%)
Inevaluable*	5 (9%)	1 (2%)	1 (2%)

*No baseline LIC measurement or no LIC measurement after baseline that could be carried forward per protocol.

In the Core protocol, the proportion of subjects with protocol deviations did not differ between arms (69% vs 64% vs 59%, p=0.54). Table 13 lists the number of deviations by broad criterion for each arm of the Core protocol. There were no significant differences between arms for any of the categories of protocol deviation.

Analysis of the primary endpoint requires an LIC by MRI at baseline and at week 52. There were 20 (12%) subjects missing either the baseline and week 52 LIC (n=1) or the LIC at week 52 (n=19). The protocol stipulated that if the week 52 LIC was missing, then the last observation after baseline would be carried forward for the primary analysis. Ten subjects missing the week 52 LIC had an earlier MRI that could be carried forward. Three additional subjects (subjects 1831_00012, 1831_00013, and 1831_00014) were treated for 14-15 months before the post baseline MRI was performed; all were in the D10 arm. The remaining six subjects without a week 52 LIC had no available LIC measurement post baseline. In total, then, there were 7 (4%) subjects inevaluable for the primary endpoint, one with no baseline LIC and six with no measurement post baseline. The majority of these subjects were in the D5 arm (Table 13).

6.1.5 Primary Efficacy Endpoints

6.1.5.1 Measurement of the Primary Endpoints

Measurement of LIC by liver biopsy is generally considered the gold standard to determine body iron burden. The primary endpoints of the A2209 Core and Extension protocols utilized MRI rather than liver biopsy to measure LIC. Study A2209 specified that LIC would be assessed by calibrated R2 MRI with post-image processing performed centrally using FerriScan, an R2 MRI analysis system cleared by FDA (K043271) and indicated "For diagnostic use to present images that reflect the magnetic resonance spectra for the determination of iron in the liver." In response to FDA's request for data to support the use of MRI rather than liver biopsy for measurement of LIC in the study population, the applicant provided summaries from two studies and data from the CICL670A0107 substudy to support the correlation between LIC by R2 MRI and by liver biopsy (Figure 3).

Figure 3: Correlation Between LIC by Liver Biopsy and FerriScan

a. Calibration Study

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St. Pierre, Clark et al, 2005

b. Validation Study

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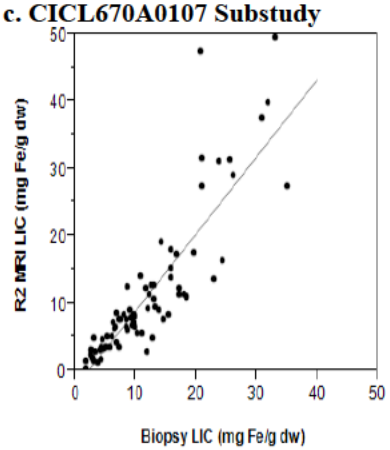
St. Pierre, El-Beshlawy et al, 2010

c. CICL670A0107 Substudy



The calibration study (St. Pierre, Clark et al, 2005) included 105 subjects age 8-74 years who were undergoing liver biopsy for iron overload or hepatitis. Forty-one (39%) of the subjects had NTDT. LIC by biopsy ranged from 0.3 to 42.7 mg Fe/g dw. The calibration curve had a Pearson correlation coefficient of 0.98. The correlation between biopsy LIC and LIC calculated from the

R2 MRI is depicted in Figure 3a. Variability of the LIC measure by MRI increased as the LIC by liver biopsy increased and with the degree of fibrosis.

The validation study (St. Pierre, El-Beshlawy et al, 2010) was a substudy of CICL670A2402, a clinical trial of deferasirox for treatment of subjects with β-thalassemia and transfusional iron overload. The cohort include 233 subjects age 3-43 years. LIC by biopsy or MRI ranged from 0.7 to 50.1 mg Fe/g dw. The correlation curve is shown in Figure 3b. The mean percentage difference between the biopsy and MRI measurements of LIC was not significantly different from zero. The correlation was robust across the five different scanners used to collect the images and across age groups.

The applicant also included data and an unpublished analysis of a substudy of CICL670A0107, a clinical trial of deferasirox for treatment of subjects with β-thalassemia with transfusional iron overload. There were 84 paired measurements from 48 subjects age 17-35 years. LIC by biopsy ranged from 1.7 to 35.1 mg Fe/g dw. The correlation curve prepared by this reviewer is shown in Figure 3c. The median difference between the biopsy and MRI measurements of LIC was 1.2 (range, -26.6 to 9.5). The mean difference was not significantly different from zero (p=0.16).

Additional input was obtained from CDRH.[F1] The CDRH consultant indicated that:

- FerriScan is an acceptable method to measure LIC in the range of 3-30 mg Fe/g dw.
- The variability of measurement of LIC by FerriScan is $\pm$10% in this range.
- The majority of variability for LIC<30 mg Fe/g dw probably results from the variability in the distribution of iron across the liver rather than variability in image acquisition, as there are quality control measures in place to minimize technical variability between scans and between scanners.
- The variability is probably larger than 10% for LICs >30 mg Fe/g dw, so small differences (i.e. -2 mg Fe/g dw) when the LIC is high may be due to the variability in measurement rather than to a true change in LIC.
- The method was able to categorize LIC above or below 3.2 mg Fe/g dw with 94% sensitivity and 100% specificity.

Reviewer Comment: Overall, the data support the use of FerriScan as an alternative to liver biopsy to measure LIC in Study A2209 to asses eligibility and treatment effect when the LIC is within the validated range. Since 8% of the randomized subjects had a baseline LIC >30 mg Fe/g dw, the impact of the variability of measurement when the LIC is high should be taken into consideration in the analysis of the primary endpoints (see Section 6.1.10.1).

6.1.5.2 Relevance of the Primary Endpoints

The primary efficacy endpoint of the Study A2209 Core Protocol was the absolute LIC change from baseline to week 52. In the intended population, asymptomatic individuals not requiring on-going transfusions, the clinical relevance of simply a reduction in LIC has not been established. By contrast, Musallam et al (Musallam, Cappellini, et al, 2011) reported in a

[F1] See Intercenter Consultation Report by Daniel Krainak, Ph.D., 7/05/2012

retrospective study that an LIC ≥6 was associated with an increased risk of complications related to iron overload (see Section 2.6).

Reviewer Comment: If the reduction in LIC induced by deferasirox were small (i.e., -2 mg Fe/g dw), the difference from baseline to end of study for a treatment arm compared to that for the placebo arm may be statistically significant without being clinically meaningful (e.g., if a subject began with a baseline LIC of 18 Fe/g dw, a reduction by -2 Fe/g dw to 16 Fe/g dw still leaves a tremendous iron burden). However, the analysis by Musallam et al suggests that reducing the LIC to less than 6 Fe/g dw may be reasonably likely to predict for a reduction in the risk of iron-related complications. In the opinion of this reviewer, then, the primary endpoint of the Study A2209 Extension protocol, a reduction in the LIC to less than 5 mg Fe/g dw, would be a relevant surrogate for a clinically meaningful treatment effect.

6.1.5.3 Analysis of the Primary Efficacy Endpoints

Achievement of LIC <5 mg Fe/g dw

The primary endpoint of the Extension protocol was the proportion of subjects who achieved an LIC <5 mg Fe/g dw at anytime on Study A2209. The analysis population was all subjects enrolled. Individuals with no posttreatment studies were considered failures. The results generated by this reviewer are shown in Table 14. For all subjects on study, 37% had an LIC <5 mg Fe/g dw at any time after start of treatment.

Table 14: Achievement of LIC <5 mg Fe/g dw On Study A2209

Population	Proportion[1]	% (95% CI)
All Subjects	61/166	37% (30-44%)
Subjects with <20 Transfusions	49/136	36% (28-44%)
All Subjects by Treatment Arm		
Deferasirox 5 mg/kg/day	17/55	31% (20-44%)[2]
Deferasirox 10 mg/kg/day	24/55	44% (31-57%)
Placebo	20/56	36% (24-49%)
In Core Protocol	2/56	4% (0-12%)
Cross Overs	18/48	38% (24-53%)

[1]Number of subjects who achieved an LIC <5 at any time after start of treatment / Total number of subjects in the group.

The current approval of deferasirox for those with transfusional hemosiderosis would cover those subjects who had received 20 or more transfusions lifetime, so this reviewer performed an exploratory analysis in the alternate subgroup, the 136 subjects who were identified as having fewer than 20 transfusions. In this subgroup, 49 of the 136 subjects (36%; 95% CI, 28-44%) achieved the target LIC, a percentage similar to that in the entire population.

The protocol also prespecified analysis of the endpoint by treatment arm in the core protocol. For the results in Table 14, the percentage of subjects who achieved the target LIC did not differ significantly across treatment arms (p=0.38). The lack of a difference between treatment arms was not necessarily due to a lack of treatment effect, since subjects were allowed to increase their deferasirox dose over the course of the study, and subjects who started on placebo were crossed over to active drug. Indeed, when the subjects from the placebo arm cross-over to active

treatment, the proportion who achieved the target LIC increased significantly (38% vs 4%, p<0.001) (Table 14).

It is acknowledged that splitting the placebo group in this manner results in a difference in follow-up times, since there would be at most 1 year of follow-up on placebo before starting open-label drug, whereas subjects on the original active treatment arms would have up to 2 years of follow-up. Since only the Core protocol has complete follow-up, results from the Core protocol alone were assessed (Table 15). The results generated by this reviewer confirmed those reported by the sponsor (120-Day Efficacy Update Table 2-2). By chi-square, the differences between treatment arms in response is significant (p=0.001). Moreover, the difference across treatment arms was significant when the baseline LIC was ≤15 mg Fe/g dw (p=0.001), including between the D5 and D10 arms (p=0.04). There was no significant difference in response across treatment arms when the baseline LIC was >15 mg Fe/g dw (p=0.37).

Table 15: Achievement of LIC <5 mg Fe/g dw at Week 52 in Study A2209 Core Protocol

	Core Protocol Starting Dose[1]		
	Deferasirox 5 mg/kg/day	**Deferasirox 10 mg/kg/day**	**Placebo**
All patients	8/55(15%)	15/55 (27%)	2/56 (4%)
Baseline LIC ≤15	8/41(20%)	14/34 (41%)	2/34 (6%)
Baseline LIC >15	0/14 (0%)	1/21 (5%)	0/22 (0%)

[1]Starting dose as randomized in the Core protocol

Reviewer Comment: The results in Table 15 clearly demonstrate that the target LIC can be achieved in a substantial proportion of NTDT patients with one year of therapy using deferasirox at a starting dose of 10 mg/kg/day, but the salutary results are driven by the subgroup having a baseline LIC is ≤15 mg Fe/g dw. There is no evidence that either of the doses tested in the Core protocol is effective when the baseline LIC is >15 mg Fe/g dw.

Additional supporting analyses prespecified in the protocol included the proportion of subjects who achieved an LIC <3 mg Fe/g dw and an LIC <7 mg Fe/g dw. An LIC <3 mg Fe/g dw, the LIC target to discontinue study drug, was reached by 13% of treated subjects (Table 16) as determined by this reviewer. It is acknowledged that since the study is on-going, the proportion of subjects who reach this LIC may differ when all subjects have completed 2 years of therapy.

Table 16: Achievement of Other Target LIC Levels On Study A2209

Population	Number	LIC <3 mg Fe/g dw	LIC <7 mg Fe/g dw
All Treated Subjects	158[1]	13% (8-19%)[2]	52% (44-60%)
Treatment Arm			
Deferasirox 5 mg/kg/day	55	11% (5-22%)	47% (35-60%)
Deferasirox 10 mg/kg/day	55	15% (8-26%)	62% (49-73%)
Placebo Only	56	0%	7% (2-17%)
Placebo Cross-Over	48	6% (5-25%)	52% (37-67%)

[1]Includes subjects who crossed over from the placebo arm..
[2]% (95% CI)

Change in LIC at One Year

The primary efficacy endpoint of Study A2209 Core protocol was the absolute LIC change from baseline at week 52 using the last available observation in the Core protocol. The median and mean changes for each treatment arm in the Core protocol as calculated by this reviewer are shown in Table 17 and confirm the results reported by the sponsor (Core protocol Clinical Study Report Table 14.2-1.9 (page 5 of 5)).

Table 17: Absolute change in LIC by Week 52 in Study A2209 Core Protocol

	Deferasirox 5 mg/kg/day (n=55)	Deferasirox 10 mg/kg/day (n=55)	Placebo (n=56)
Median change in LIC (range)	-2.0* (-9.1 - +6.7)	-3.3 (-12.0 - +4.8)	+0.1 (-8.1 - +10.7)
Mean change in LIC (95% CI)	-1.9 (-2.7, -1.0)	-3.8 (-4.9, -2.6)	+0.3 (-0.7. +1.2)
ANCOVA			
p-value vs placebo	p=0.001	p<0.001	
p-value 5 mg/kg vs 10 mg/kg		p=0.009	

*All values provided as mg Fe/g dw.

The change in LIC from baseline to week 52 was statistically significant across the treatment arms (Table 17) (p<0.001). Additional analyses that were prespecified included comparisons between each active treatment arm and placebo, and between the two active treatment arms. As shown in Table 17, a significant treatment effect relative to placebo was seen for both treatment arms, and the effect in the D10 arm was significantly greater than that in the D5 arm.

Reviewer Comment: The Core protocol met its primary objective and is a positive study. The absolute change in LIC over one year as shown in Table 17 clarifies why only a percentage of subjects achieved the target LIC. The relatively small change in LIC (median -3.3 mg Fe/g dw in the D10 arm) would not be a sufficient decrease to allow subjects with an LIC >15 mg Fe/g dw to reach the target LIC in one years, and in fact, even two years of treatment using 10 mg/kg/day would not be expected to be sufficient.

6.1.6 Subpopulations

Achievement of LIC <5 mg Fe/g dw

The sponsor provided no subpopulation analyses for achievement of the target LIC. Since the study was on-going and the follow-up data were incomplete, this reviewer assessed the treatment effect by subpopulation using a proportional hazard model for time to LIC <5 mg Fe/g dw to account for the differences in time to endpoint assessment. The subgroups assessed individually as covariates included age (<17 vs ≥17 years), gender, race, thalassemia diagnosis, splenectomy, number of prior transfusions (0 vs 1-19 vs ≥20) and prior chelation therapy. Baseline LIC (<7 vs 7-15 vs >15 mg Fe/g dw) and starting dose of deferasirox (5, 10 or 20 mg/kg/day) were included in the model for each subgroup analysis (i.e., trivariate analyses). None of the covariates listed

had a p-value ≤0.01, but baseline LIC and starting dose of deferasirox both maintained p-values ≤0.01 in each of the trivariate analyses (Table 18).

Table 18: Achievement of LIC < 5 mg Fe/g dw by Subpopulation

Covariate	Subgroup	Risk Ratio	(95% CI)	p-Value for Covariate[1]	p-Value for LIC[1]	p-Value for Dose[1]
Age	Adult	1.00	.		<0.001	0.004
	< 17 years	0.42	(0.15-0.96)	0.04		
Gender	Male	1.00			<0.001	0.001
	Female	1.46	(0.85-2.48)	0.17		
Race	Caucasian	1.00			<0.001	0.002
	Asian	0.56	(0.13-1.63)	0.32		
	Other	0.62	(0.35-1.09)	0.10		
Diagnosis	β-Thalassemia	1.00			<0.001	0.002
	Hgb E β-Thalassemia	0.66	(0.33-1.25)	0.20		
	α-Thalassemia	2.01	(0.98-3.90)	0.06		
Splenectomy	No	1.00			<0.001	0.002
	Yes	1.03	(0.60-1.77)	0.91		
Transfusions	0	1.00			<0.001	0.002
	1-19	0.53	(0.28-1.04)	0.06		
	≥20	0.57	(0.24-1.33)	0.19		
Prior Chelation	No	1.00			<0.001	0.004
	Yes	1.02	(0.54-1.82)	0.96		

[1]Each analysis included baseline LIC and dose in addition to the covariate listed.

Change in LIC at One Year

The sponsor provided descriptive subgroup analyses (by age, gender, race, baseline LIC, baseline ferritin, history of splenectomy, primary diagnosis and number of prior transfusions) of absolute change in LIC at week 52 in the Core protocol. In contrast to their respective comparators, the treatment effect was numerically higher in those ≥18 years of age, female, having a baseline LIC >15 mg Fe/g dw, and with no prior splenectomy. The sponsor also noted that the treatment effect was dose-dependent across all subgroups except for those subjects with alpha-thalassemia, which was a small subgroup (21 subjects divided among the three treatment arms). No statistical analyses were performed.

Reviewer Comment: The subgroup analysis suggests that the treatment effect does not differ across the subgroups assessed when LIC and deferasirox dose are taken into account. There is a marginal effect by age, but given the multiple comparisons, the p-value must be interpreted with caution.

6.1.7 Analysis of the Secondary Efficacy Endpoints

Changes in several measures of iron burden, iron metabolism and erythropoiesis served as secondary endpoints. The mean absolute changes in these parameters during the Core protocol by randomized arm as determined by this reviewer are shown in Table 19.

Table 19: Analysis of Secondary Endpoints in Study A2209 Core[1]

Analyte Assessed For Mean Change	Placebo	Deferasirox 5 mg/kg/day	Deferasirox 10 mg/kg/day	p-value
Ferritin (ug/L)	73	-115	-249	0.002
(95% CI)	(-53 - 200)	(-242 - 11)	(-377 - 121)	
Iron (umol/L)	0.7	1.2	1.9	0.61
(95% CI)	(-1.1 - 2.4)	(-0.5 - 3.0)	(1.2 - 3.7)	
Transferrin (g/L)	0.03	0.10	0.17	0.003
(95% CI)	(-0.02 - 0.09)	(0.04 - 0.16)	(0.12 - 0.24)	
Transferrin Saturation (%)	2.2	-7.0	-3.6	<0.001
(95% CI)	(-0.5 - 4.8)	(-9.8 - -4.2)	(-6.4 - -0.8)	
Soluble Transferrin Receptor	1.6	1.2	1.0	0.79
(mg/L) (95% CI)	(0.2 - 2.9)	(-0.2 - 2.5)	(-0.4 - 2.3)	
Labile Plasma Iron (U)	0.01	-0.07	-0.08	0.15
(95% CI)	(-0.05 - 0.09)	(-0.14 - 0)	(-0.15 - 0)	
Nontransferrin Bound Iron	-0.1	-0.8	-0.7	0.21
(umol/L) (95% CI)	(-0.7 - 0.5)	(-1.4 - -0.2)	(-1.3 - -0.1)	
Erythropoietin (U/L)	49	59	-43	0.53
(95% CI)	(-90 - 187)	(-83 - 200)	(-183 - 96)	
Hepcidin (nmol/L)	-0.1	-0.3	-2.4	0.36
(95% CI)	(-2.6 - 2.4)	(-2.9 - 2.3)	(-4.9 - 0.1)	
Growth Differentiation Factor 15	1934	966	-447	0.22
(ng/L) (95% CI)	(40-3827)	(-967 - 2899)	(-2360 - 1466)	
Haptoglobin (g/L)	0	0	0	0.69
(95% CI)	(-0.02 - 0.02)	(-0.03 - 0.01)	(-0.03 - 0.01)	
Hemoglobin (g/L)	-2.7	-1.9	-1.0	0.38
(95% CI)	(-4.6 - -1.0)	(-3.7 - -0.1)	(-2.8 - 0.8)	
Reticulocytes (x 10^9/L)	24.9	18.9	17.2	0.84
(95% CI)	(6.2 - 43.5)	(-0.3 – 38.1)	(-1.8 - 36.2)	

[1]Mean absolute change (95% CI) from baseline to month 12

There were significant dose-related reductions in ferritin (p=0.002) and transferrin (p=0.003), and a treatment-related reduction in transferrin saturation (p<0.001) (Table 19). Several dose-related but nonsignificant trends were noted, including an increase in serum iron and reductions in labile plasma iron, and nontransferrin bound iron. There also appeared to be less reduction in hemoglobin and less increase in reticulocytes in the two active treatment arms in comparison to placebo, although the differences were not significant.

There were nonsignficant dose-related trends in the changes in hepcidin and growth differentiation factor 15 (Table 19), but the changes seen did not reflect normalization of these factors after treatment. When comparing measurements at baseline to month 12, the erythropoietin level was elevated in 94% vs 96% of subjects treated with deferasirox, the growth differentiation factor 15 was elevated in 98% vs 100%, and the hepcidin level was below the lower limit of normal in 19% vs 32%.

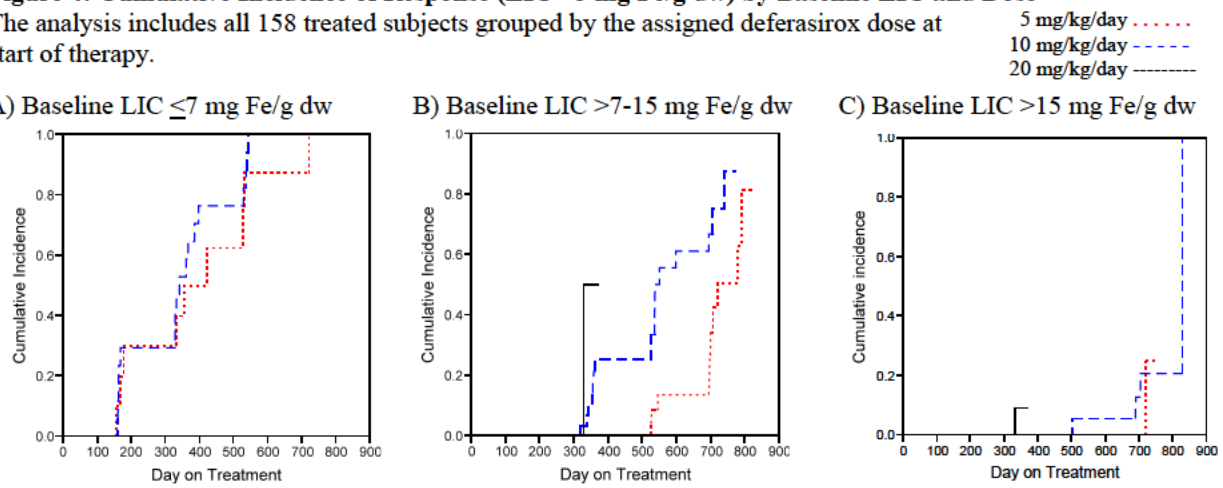
Reviewer Comment: The changes in iron burden across treatment arms are consistent with the treatment effect of deferasirox. The changes in iron metabolism parameters (erythropoietin, hepcidin and growth and differentiation factor 15) are noninformative.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

6.1.8.1 Dose-Response

The impact of the starting dose of deferasirox on achievement of target LIC (LIC <5 mg Fe/g dw) and on the absolute change in LIC in the Core protocol was described in Section 6.1.5.3. Further subgroup analyses in Section 6.1.6 identified only deferasirox dose and baseline LIC as predictors of response. Figure 4 shows graphically the impact of starting deferasirox dose by baseline LIC on time to achieve the target LIC for all 158 treated patients.

Figure 4: Cumulative Incidence of Response (LIC <5 mg Fe/g dw) by Baseline LIC and Dose
The analysis includes all 158 treated subjects grouped by the assigned deferasirox dose at start of therapy.



Reviewer Comment: Figure 4A and B clearly demonstrate the activity of the 10 mg/kg/day starting dose when the baseline LIC is <15 mg Fe/g dw. The few responders in Figure 4C with baseline LIC being >15 mg Fe/g dw were either started on or escalated to the 20 mg/kg/day dose. This further supports use of the baseline LIC to choose the starting dose in order to be able to achieve the target LIC is a reasonable period of time. The benefit of the 20 mg/kg/day dose will also need to be confirmed, since the available follow-up at this dose is incomplete.

6.1.8.2 Use of Ferritin as a Surrogate for LIC

The sponsor proposes to use serum ferritin level <300 ng/mL as an alternative to LIC measurement to determine when deferasirox should be discontinued. The sponsor undertook an analysis of 2067 paired LIC and ferritin measures from four prior clinical trials. The resulting adjusted r^2 from simple linear model was 0.55. The sponsor concluded that there was a correlation between ferritin and LIC, but prediction at the individual level was weak.

This reviewer identified in the Study A2209 data files 561 LIC measurements performed within 14 days with a serum ferritin performed in the same subjects. An analysis of correlation between LIC and ferritin showed an r^2=0.43. There were 23 cases with an LIC <3 mg Fe/g dw. Of these, only 10 had a serum ferritin less than 300 ng/mL. A ferritin <300 ng/mL had a 97%

sensitivity but only a 44% specificity for identifying when the LIC was <3 mg Fe/g dw. This reviewer agrees with the sponsor's conclusion that a single serum ferritin measurement does not accurately predict the LIC. As such, ferritin alone is not a reliable method to provide guidance for dose modifications of deferasirox.

Reviewer Comment: Study A2209 was not designed to test the safety and efficacy of treatment with deferasirox guided solely by serum ferritin, and the predictive value of the test based on the data available do not support use of serum ferritin as a surrogate for LIC to guide treatment in the NTDT population. The instructions for use should reflect the need for use of LIC to ensure safe use. It would probably be acceptable to use serum ferritin as a screening tool if LIC by biopsy or MRI were used was confirmation.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Since the protocol prespecified dose modifications for efficacy every six months, the duration of follow-up on any particular dose is relatively short. Hence, a meaningful analysis of the persistence of efficacy of any given dose could not be performed with the data available.

6.1.10 Additional Efficacy Issues/Analyses

6.1.10.1 Error of Measurement

As indicated in Section 6.1.5.1, there is approximately a 10% error in the measurement of LIC by MRI. There were no subjects who achieved an LIC <5 mg Fe/g dw by reduction in LIC that was less than 10% of the baseline, so the results of the primary endpoint of the Extension protocol are presumed to be accurate.

The absolute change in LIC at week 52 was less than 10% of the baseline LIC for 23% of the subjects, including 19% on deferasirox 5 mg/kg, 2% on 10 mg/kg, and 44% on placebo. The high rate of change in LIC less than 10% in the placebo group suggests that it is possible that much of the absolute change in LIC seen in that group may be due to error in measurement.

6.1.10.2 Assessment for Bias

The investigators at three clinical sites (0404, 0801 and 1831) were noted to have a financial conflict of interest (see Section 3.3). To determine whether there was a potential for bias in the outcomes at these sites, a comparison was made between the outcomes at these sites and the remainder of the clinical sites for the study. The percentage of subjects in the treatment arms who achieved an LIC <5 mg Fe/g dw at the centers with a financial conflict of interest was higher than at the other clinical sites (50% vs 33%); however, when dose of deferasirox and baseline LIC were taken into account, there was no significant difference in the cumulative incidence of subjects who achieved an LIC <5 mg Fe/g dw at the centers with a financial conflict of interest (p=0.71) in comparison to the other clinical sites.

Reviewer Comment: The analyses in Sections 6.1.20.1 and 6.1.10.2 show no evidence that the primary efficacy endpoints were affected by errors in LIC measurement or by bias from the

investigators with financial conflicts of interest. This reviewer therefore concludes that the integrity of the conclusions from the efficacy analyses is preserved.

6.1.11 Literature Review

Two pilot studies were published that described use of deferasirox for treatment on NTDT, mainly thalassemia intermedia.

Voskaridou et al (Voskaridou, Plata 2009) treated 11 subjects having an LIC >3 mg Fe/g dw starting deferasirox at 10-20 mg/kg. Doses were escalated to 20 mg/kg in 9 subjects and to 30 mg/kg in two. Ten subjects had an LIC measured before and after 12 months of therapy. The mean absolute change in LIC was -5.6 mg Fe/g dw. One (14%) of 7 evaluable subjects achieved an LIC <5 mg Fe/g dw, and one (10%) of 10 evaluable subjects achieved an LIC <3 mg Fe/g dw at 12 months.

Ladis et al (Ladis, Berdousi 2010) treated 11 subjects having an LIC >2 mg Fe/g dw starting deferasirox at 10-20 mg/kg. The dose was escalated to 25 mg/kg in one subject with a very high baseline LIC. One subject dropped out early, 1 was taken off therapy after 12 months when the LIC was <2 mg Fe/g dw, and the remaining nine subjects completed 24 months of treatment. The absolute change in mean LIC was -5.2 mg Fe/g dw at 12 months and -11.3 mg Fe/g dw at 24 months. Three (30%) subjects achieved an LIC <5 mg Fe/g dw at 12 months, and seven (70%) at 24 months. Five (50%) achieved an LIC <3 mg Fe/g dw at 24 months.

Reviewer Comment: Although there was not sufficient detail in the publications to assess the impact of starting dose and baseline LIC on outcome, both pilot studies showed that patients treated with deferasirox for 1-2 years achieved the target LIC levels, supporting the efficacy analysis of Study A2209.

6.1.12 Efficacy Findings from Study A2209 Extension Protocol Final Report

Additional analyses of the Extension protocol data were received by the FDA on 11/29/2012, the final study report for the Extension protocol was received on 11/30/2012, and the datasets were received 12/5/2012. The following analyses represent new information to be considered an addendum to the review above.

6.1.12.1 Extension Protocol Demographics and Disposition

There were 133 subjects from the Study A2209 Core protocol who enrolled on the Extension protocol, including 85 subjects who continued from the active treatment arms and 48 subjects who crossed over from the placebo groups. The demographic characteristics from start of the study are shown in Table 20. The baseline LIC for the extension protocol was <3 mg Fe/g dw for 3 (2%) subjects, 3 to <5 mg Fe/g dw for 17 (13%) subjects, 5-15 mg Fe/g dw for 70 (53%) subjects, and >15 mg Fe/g dw for 43 (32%) subjects.

Table 20: Characteristics of Subjects in the Study A2209 Extension Protocol

	All Subjects (n=133)
Median Age (range)	32 (10 - 69) yrs
Age <17 years	14 (11%)
Gender Male	73 (55%)
Female	60 (44%)
Race White	68 (51%)
Asian	62 (47%)
Black	2 (2%)
Other	1(1%)
Diagnosis β-Thalassemia	69 (52%)
Hgb E β-Thalassemia	45 (34%)
α-Thalassemia	19 (14%)
Prior Splenectomy	68 (51%)
Prior Transfusions	116 (87%)
Median Number of Transfusions (range)	8 (1-75)
Prior Chelation Therapy	40 (30%)
Median Extension Baseline LIC (range)	10.9 (1.2 – 46.4) mg Fe/g dw

Of the 133 subjects in the Extension protocol, 130 subjects were treated with deferasirox, and 3 subjects with low baseline LICs were observed without active treatment. Of the subjects treated with deferasirox, 3 (2%) discontinued early as described previously in Table 10, and the remainder completed the protocol.

6.1.12.2 Extension Protocol Efficacy Analysis

There were 113 subjects in the Extension protocol with a baseline LIC ≥5 mg Fe/g dw who could be evaluated for achievement of the target LIC at Week 52. The sponsor reported that in the Extension protocol, 39 (35%) of the 113 evaluable subjects achieved an LIC <5 mg Fe/g dw by Week 52 of treatment with deferasirox (Additional Analyses Table 2-11), and this reviewer confirmed these results. There was no significant difference in the response rate by whether the subject was continuing from an active treatment arm in the Core protocol or crossing over from placebo (30% of continuing subjects vs 40% of crossovers, p=0.32), so further analyses of the extension protocol were not split out by these subgroups.

According to the design of the Extension protocol, the baseline LIC was taken into account when the deferasirox dose was assigned at the start of treatment. The results by baseline LIC and planned starting dose of deferasirox are shown in Table 21. The target LIC was reached by 51% of those treated with the 10 mg/kg/day dose when the baseline LIC was ≤15 mg Fe/g dw, and by 10% of those treated with the 20 mg/kg/day dose when the baseline LIC was >15 mg Fe/g dw (Table 21).

Table 21: Efficacy Outcomes at Week 52 in the Study A2209 Extension Protocol

	Extension Protocol Planned Starting Dose[1]		
	Deferasirox 5 mg/kg/day	**Deferasirox 10 mg/kg/day**	**Deferasirox 20 mg/kg/day**
Achievement of LIC <5 mg Fe/g dw			
All evaluable patients[2]	3/5 (60%)	31/65 (48%)	5/43 (12%)
Baseline LIC ≤15	3/5 (60%)	31/61 (51%)	1/4 (25%)
Baseline LIC >15	-	0/4 (0%)	4/39 (10%)
Median change in LIC[3] (range)	-1.7 (-4.9 to +3.0)	-2.4 (-11.7 to +3.9)	-8.9 (-23.1 to +2.1)
Mean change in LIC[3] (95% CI)	-1.5 (-3.7 to +0.7)	-2.8 (-3.4 to -2.2)	-9.1 (-11.0 to -7.3)

[1]Starting dose as assigned in the Extension protocol
[2]For the 113 treated subjects with a baseline LIC ≥5 mg Fe/g dw in the Extension Protocol
[3]For the 130 treated subjects, data were available for 8 of 9 subjects assigned to 5 mg/kg/day, 77 of 78 assigned to 10 mg/kg/day, and all 43 assigned to 20 mg/kg/day

6.1.12.3 Overall Study A2209 Core plus Extension Efficacy Analysis

The sponsor reported that 64 (39%) of the 166 subjects enrolled on the study achieved an LIC <5 mg Fe/g dw during either the Core or Extension protocol (Extension Protocol Clinical Study Report Table 11-5). This reviewer confirmed that 64 subjects achieved the target LIC, but calculated the rate as 63 (41%) of 158 subjects when assessed as the proportion of those treated with active drug. This included 43 (39%) of the 110 subjects on active treatment for up to two years, and 20 (42%) of the 48 subjects in the crossover group.

The subgroup analysis in Section 6.1.6 raised a question regarding the outcomes in children. This was assessed further by calculating the response rate by age group. The target LIC was reached by 7 (44%) of 16 children and 56 (39%) of 152 adults treated with deferasirox in either the Core or Extension protocol (p=0.79).

The sponsor reported that 24 (15%) of the 166 subjects enrolled on the study achieved an LIC <3 mg Fe/g dw during either the Core or Extension protocol (Extension Protocol Clinical Study Report Table 11-5). This reviewer confirmed that 24 subjects achieved this LIC and interrupted treatment with study drug.

Reviewer Comment: The final results of the Extension protocol confirm the previous findings that a substantial proportion of patients with a baseline LIC ≤15 mg Fe/g dw can achieve the target LIC with 1 year of treatment with deferasirox 10 mg/kg/day, the absolute reduction in LIC per year is dose-dependent, and it is expected that 2 or more years of treatment with deferasirox at 20 mg/kg/day will be needed to achieve a response when the baseline LIC is >15 mg Fe/g dw.

7 Review of Safety

Safety Summary

The safety dataset include 158 subjects with NTDT treated with deferasirox who were treated for up to two years. The Core protocol and the Extension protocol were one year in duration. Dose increases were prespecified during the course of treatment, and exposure varied by subject. The dose of 10 mg/kg/day was used for some period of time by most subjects. The safety data set also includes information for 56 subjects treated with placebo for one year. The population was monitored for deaths, serious adverse events, adverse events of interest, common adverse events, critical laboratory test results, common laboratory tests, ECGs, auditory testing and ocular exams. Analysis of the safety data showed:

- There were no deaths.
- Gastroenteritis (4%), anemia (4%), abdominal pain (3%) and pyrexia (3%) were the most common SAEs. Two SAEs (rash and hepatotoxicity) were considered to be related.
- The most common suspected AEs (≥5% in either protocol) are diarrhea, rash and nausea.
- Twenty-four subjects achieved an LIC <3 mg Fe/g dw after start of treatment. The only suspected AEs that occurred in this population with an incidence ≥5% more than in those not achieving an LIC <3 mg Fe/g dw were nausea (13% vs 4%) and abdominal pain upper (8% vs 3%).
- A renal adverse event of interest was identified in 2-4% of treated subjects, 2-3% had a sustained creatinine more than 133% above baseline, and 2-3% had a creatinine clearance <60 mL/min. The percentage of subjects with a creatinine-related adverse event was dose-dependent. In addition, there was a significant increase in creatinine and a decrease in creatinine clearance over 2 years of treatment. The deterioration in renal function in NTDT subjects treated with deferasirox for 2 years was also reported in the literature.
- Transaminases generally decreased over 2 years of therapy, but there were 3 hepatic SAEs that were suspected, and 1-2% of the subjects had a critical increase in AST or ALT.
- The SOC Gastrointestinal disorder was the SOC with the highest number of events not caused by infection. The percentage of subjects with a gastrointestinal-related adverse event was dose-dependent, and 1-2% of subjects had a gastrointestinal event of interest.
- Rash was the one of the most common suspected AEs, and there was one rash reported as an SAE that was considered related to deferasirox.
- A hearing loss adverse event of interest was identified for 1-2% of subjects. Hearing loss events were more common in subjects treated with chelation therapy prior to start of study.

- There were three suspected AEs with ocular abnormalities (2 with cataracts and 1 with conjunctivitis).

- There were four significant changes identified on ECG (atrial fibrillation, left ventricular hypertrophy, interventricular conduction delay, and tachyarrhythmia). There was also an increase in what was termed clinically insignificant ECG changes, but these were not identified in the application.

- There were no cases of multilineage cytopenia and no differences in hematological critical laboratory results between the treated subjects and the placebo group. There was a trend for a decrease in hemoglobin over 2 years of treatment, but as shown in the analysis of secondary endpoints Section 6 above, the reduction in hemoglobin in the treated subjects was less than that in the placebo group.

- There was no evidence for an increased rate of AEs in children as compared to adults. Additionally, the rate of increase in creatinine in children was less than in adults. There are no data on the impact of treatment on growth and development in children with NTDT.

Overall, the safety profile of deferasirox in the NTDT subjects was similar to that seen in patients with thalassemia major. No new adverse events were identified. The analysis is limited by the short follow-up at any given dose. There are also no data on whether deferasirox will alter growth and development in children when administered without concomitant transfusion therapy.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Clinical review of safety for this NDA was based on the safety data presented in Study A2209 and safety data presented in Study A2202. Table 7 in Section 5.1 describes the two studies. Safety data were available for 166 subjects in Study A2209 and 49 subjects from Study A2202.

7.1.2 Categorization of Adverse Events

Adverse events for studies A2209 and A2202 were reported down to the verbatim term. The adverse events were coded using MedDRA version 14.1 for Study A2209 and version 12.0 for Study A2202.

Nine categories of adverse events of special interest were prespecified based on safety signals from prior deferasirox clinical trials. The search strategies used for each category is shown in Table 22.

Table 22: Search Strategies for Adverse Events of Special Interest

Adverse Event of Special Interest	Search Level[1]	Terms
Increased serum creatinine	PT	Blood creatinine abnormal Blood creatinine increased Glomerular filtration rate abnormal Glomerular filtration rate decreased Hypercreatininaemia
Renal tubular disorders	HLT	Nephropathies and tubular disorders NEC
Acute renal failure	SMQ	Acute renal failure (broad) Minus the following PTs: Blood creatinine abnormal Blood creatinine increased Glomerular filtration rate abnormal Glomerular filtration rate decreased Hypercreatininaemia Renal tubular disorder
Increased liver transaminases	PT	Alanine aminotransferase abnormal Alanine aminotransferase increased Aspartate aminotransferase abnormal Aspartate aminotransferase increased Hepatic enzyme abnormal Transaminases abnormal Transaminases increased
Hepatic failure	SMQ	Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (severe events only) (broad)
Hearing loss	HLT	Hearing losses Auditory function diagnostic procedures
Lens opacities, retinal changes and optic neuritis	PT HLT	Optic neuritis Cataract conditions Lens structural change, deposit and degeneration Retinal bleeding and vascular disorders Retinal structural change, deposit and degeneration Retinal, choroid and vitreous infections and inflammations Retinopathies NEC
Gastrointestinal haemorrhage and ulcers; oesophagitis	PT SMQ	Oesophagitis Gastrointestinal haemorrhage Gastrointestinal ulceration
Peripheral blood cytopenias	SMQ	Haematopoietic cytopenias affecting more than one type of blood cell (narrow) Haematopoietic leukopenia (narrow) Haematopoietic thrombocytopenia

[1]PT, preferred term; HLT, higher level term; SMQ, standardized MedDRA query

7.1.3 Pooling of Data

The sponsor included safety data from both studies A2209 and A2202 in their submission. The patient populations studied in the two studies are considerably different and have different risk profiles. Study A2209 is the only placebo-controlled trial that has been conducted by Novartis in the development of deferasirox and allows for a more rigorous safety review. As such, the

review of safety presented will focus largely on the results reported for study A2209. Study A2202 is a single arm trial for treatment of hereditary hemochromatosis, a different patient population than the proposed indication, NTDT. Notable safety events from study A2202 are reported here (Section 7.7.2), but due to the differences in the patient populations and MedDRA versions used for coding, data from the two studies were not pooled.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses

There were 158 subjects with NTDT who were treated with varying doses of deferasirox on Study A2209. Demographics by dose are shown in Table 9.

Reviewer Comment: There is no characterization of individuals with NTDT in the US to use as a comparison in order to determine if the study population is representative of such patients in the US. Moreover, 16% of the study population had transfusional hemosiderosis resulting from 20 or more life-time transfusions, a group with a somewhat different natural history from NTDT, especially with regard to cardiac complications, and this will need to be considered in the analysis of the adverse events. In addition, although 158 subjects is a relatively small safety dataset, it is acknowledged that the number of patients in the US with NTDT is also small. Of greater concern is the fact that the Study A2209 follow-up is only 2 years, which is a relatively short follow-up for a drug that is to be taken chronically and potentially life-long.

7.2.2 Explorations for Dose Toxicity Relationship

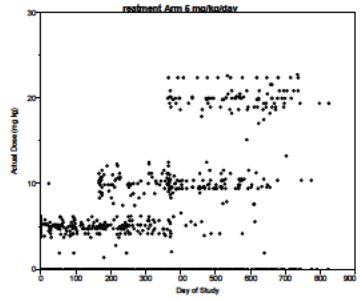
A total of 158 subjects received active drug (110 subjects randomized in the Core protocol and 48 subjects who crossed over from placebo to open-label drug in the Extension protocol). Exposure data was obtained from the Medication Administration Record. There was a median of 10 entries per subject. Some subjects were still on treatment when the dataset was locked. Missing end dates of treatment for such subjects was imputed to the last visit date.

Deferasirox was to be taken daily for 12 months on the Core protocol and for an additional 12 months (24 months total) on the Extension protocol. For all subjects, the median duration of therapy was 592 days (range 5-824 days). The median duration of therapy was 699 days (range 5-824 days for subjects on the D5 arm, 700 days (range 57-811 days) for subjects on the D10 arm, and 355 days (range 84-370 days) for subjects from the placebo arm who crossed over to open label deferasirox.

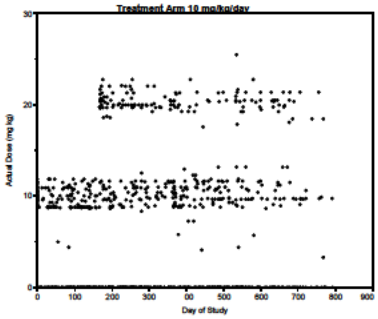
At the start of the Core protocol, subjects were randomized to 5 mg/kg/day or 10 mg/kg/day. The dose was modified based on LIC at three time points across the Core and Extension protocols (Section 5.3.1): (a) At week 24, the dose was doubled if the LIC was $\leq$7 Fe/g dw and the change in LIC was <15%. (b) At month 12, the dose was modified based on LIC cut points of 3 and 15 mg Fe/g dw and if the change in LIC was <30%, with a maximum dose of 20 mg/kg/day. (c) At month 18, the dose was modified based on LIC cut points of 3 and 7 mg Fe/g dw and if the change in LIC was <15%, with a maximum dose of 20 mg/kg/day.

Figure 5: Recorded Actual Deferasirox Doses Over Time by Assigned Arm in Core Protocol

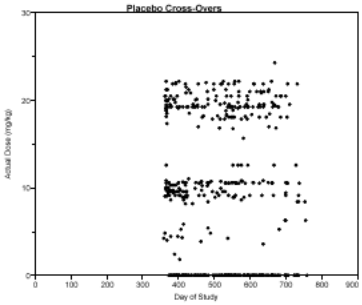
a) Treatment Arm 5 mg/kg/day



b) Treatment Arm 10 mg/kg/day



c) Placebo Cross-overs



The actual doses recorded are shown in Figure 5. Dose increases occurred in both active treatment arms in the Core protocol at the protocol-specified time points as described above.

By the end of the Extension protocol, 82% of the subjects originally assigned to D5 had escalated the dose, and 58% of the subjects originally assigned to D10 had escalated (Table 23). In the extension study, 62% of the placebo crossovers were in 20 mg/kg/day actual dose group. One subject had received 39.8 mg/kg/day in error.

Table 23: Maximal Deferasirox Dose Used by Treatment Arm in Core Protocol

	Treatment Arm in Core Protocol		
Maximal Actual Deferasirox Dose Group[1]	**Deferasirox 5 mg/kg/day (n=55)**	**Deferasirox 10 mg/kg/day (n=55)**	**Placebo Cross Overs (n=48)**
In Core Protocol			
5 mg/kg	27 (49%)	0	-
10 mg/kg	28 (51%)	30 (55%)	-
20 mg/kg	0	25 (45%)	-
In Core plus Extension Protocol			
5 mg/kg	10 (18%)	0	0
10 mg/kg	27 (49%)	23 (42%)	18 (38%)
20 mg/kg	18 (33%)	32 (58%)	30 (62%)

[1]Maximal deferasirox dose recorded in the group indicated as 5 mg/kg/day (median 5, range 1.4-7.3), 10 mg/kg/day (median 10, actual 7.5-14.9), 20 mg/kg/day (median 20, range 15.2-39.8).

The analysis of actual doses shows that there is substantial overlap in the doses used in the D5 arm and the D10 arm, so differences in toxicities by treatment arm that would reflect the randomized dose may not be detectable. It does, however, support pooling the arms to improve the estimate of risks of adverse events.

In addition to the protocol-specified dose modifications for LIC, doses could be reduced or interrupted for toxicities. Details on dose modifications and discontinuations are provided in Section 7.3.3. The set size of the tablets also limited the accuracy of dosing. For all recorded actual doses, 61% were at least 80% of the dose prescribed by protocol. The median percentage

of the prescribed dose administered was 93% for the D5 arm, 91% for the D10 arm and 91% for the placebo cross overs.

Table 24: Study Drug Exposure

		Grouped by Actual Dose[2]		
Months	**On Study**	**5 mg/kg[2]**	**10 mg/kg[2]**	**20 mg/kg[2]**
0-3	158 (100%)[1]	77 (100%)	130 (100%)	80 (100%)
4-6	153 (97%)	53 (69%)	117 (90%)	72 (90%)
7-9	151 (96%)	33 (62%)	89 (69%)	53 (66%)
10-12	138 (87%)	24 (31%)	71 (55%)	31 (39%)
13-15	99 (63%)	11 (14%)	41 (32%)	9 (11%)
16-18	84 (53%)	4 (5%)	29 (22%)	5 (6%)
19-21	83 (52%)	4 (5%)	12 (9%)	0 (0%)
22-24	70 (44%)	3 (4%)	7 (5%)	0 (0%)

[1]Number (%)
[2]Group by actual dose indicated as 5 mg/kg/day (median 5, range 1.4-7.3), 10 mg/kg/day (median 10, actual 7.5-14.9), 20 mg/kg/day (median 20, range 15.2-39.8)

Table 24 shows the duration on study with active drug for all 158 treated subjects and the breakdown of cumulative days grouped by actual dose. The actual daily doses varied from 1.4-39.8 mg/kg; these doses were categorized by range as 5 mg/kg (median 5, range 1.4-7.3), 10 mg/kg (median 10, actual 7.5-14.9), 20 mg/kg (median 20, range 15.2-39.8).

7.2.3 Special Animal and/or In Vitro Testing

There is no new nonclinical information in this supplement.

7.2.4 Routine Clinical Testing

Clinical safety evaluations were scheduled for every 4 weeks during the Core and Extension protocols, and weekly for four weeks after each dose increase. This schedule of safety evaluations was considered adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

No formal clinical pharmacological studies were conducted in the NTDT population. A pharmacokinetics analysis from Study A2202 in the hereditary hemochromatosis subjects was included in this supplement. No additional safety concerns were identified in the pharmacokinetics study that would be applicable to the NTDT population.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The most common serious adverse events attributed to deferoxamine are ocular and auditory toxicities (Section 2.4). Subjects in Study A2209 had ocular and auditory exams at screening, at the end of the Core protocol, and at the end of the Extension protocol (Section 7.4.5). Growth inhibition in children treated with chelation therapy was also reported in the literature, but the length of follow-up in Study A2209 would not be sufficient to assess growth and development.

The most common serious adverse events attributed to deferiprone are neutropenia and elevated hepatic enzymes. Monitoring for such events in Study A2209 is described in section 7.2.4.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in Study A2209.

7.3.2 Nonfatal Serious Adverse Events

There were 48 SAE reports for 38 subjects throughout the study duration. A tabulation of events by preferred term is shown in Table 25. Gastroenteritis, anemia, abdominal pain and pyrexia were the most common SAEs in the treated population, and these did not occur as SAEs in the subjects treated with placebo. It is noted that follow-up for the placebo group is shorter than that for the treated subjects.

Table 25: Serious Adverse Events For Study A2209

	Up to 2 Years Follow-up				Up to 1 Year Follow-up					
	Deferasirox[1] 5 mg/kg/day (n=55)		Deferasirox[1] 10 mg/kg/day (n=55)		Cross Overs (n=48)		Placebo[1] (n=56)		All Treated (n=158)	
Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any Event	**10**	**18**	**13**	**24**	**9**	**18**	**8**	**14**	**32**	**20**
Gastroenteritis	2	4	4	7	1	2			7	4
Anemia	1	2	2	4	3	6			6	4
Abdominal pain	1	2	2	4	1	2			4	3
Pyrexia			3	5	1	2			4	3
Gastritis			2	4					2	1
Cholangitis			1	2	1	2			2	1
Pregnancy	1	2	1	2					2	1
Hemolysis			1	2					1	1
Atrial fibrillation			1	2					1	1
Atrial septal defect	1	2							1	1
Cataract	1	2							1	1
Abdominal tenderness			1	2					1	1
Duodenal ulcer			1	2					1	1
Dyspepsia					1	2			1	1
Pancreatitis acute			1	2					1	1
Cholecystitis acute			1	2					1	1
Cholecystitis chronic					1	2			1	1
Cholelithiasis			1	2			1	2	1	1
Hepatitis					1	2			1	1
Hepatotoxicity	1	2							1	1
Portal vein thrombosis	1	2							1	1
Babesiosis					1	2			1	1
Cellulitis	1	2							1	1
Influenza			1	2					1	1
Liver abscess					1	2			1	1

Table 25: Serious Adverse Events For Study A2209

	Up to 2 Years Follow-up				Up to 1 Year Follow-up					
	Deferasirox[1] 5 mg/kg/day (n=55)		Deferasirox[1] 10 mg/kg/day (n=55)		Cross Overs (n=48)		Placebo[1] (n=56)		All Treated (n=158)	
Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Osteomyelitis			1	2					1	1
Pneumonia					1	2	1	2	1	1
Helicobacter gastritis			1	2					1	1
Respiratory tract infection	1	2							1	1
Road traffic accident			1	2					1	1
Pelvic fracture	1	2							1	1
Upper limb fracture			1	2					1	1
C-reactive protein	1	2							1	1
Syncope	1	2							1	1
Ovarian cyst			1	2					1	1
Ovarian cyst ruptured					1	2			1	1
Pruritus			1	2					1	1
Rash			1	2					1	1
Arrhythmia							1	2		
Cholecystitis							1	2		
Dengue fever							1	2		
Viral upper respiratory infection							1	2		
Tibia fracture							1	2		
Dehydration							1	2		
Optic neuritis							1	2		

[1]Randomized arm in the Core protocol

There were six SAEs considered at least possibly related to the study drug by the applicant.

1. *Subject 0701 00001* (D5 arm) was hospitalized with severe abdominal pain and vomiting after 4.5 months of treatment with deferasirox 5 mg/kg/day. A specific etiology was not identified, and the event resolved in 2 days with hydration and symptomatic treatment and no change in study drug. Microcholelithiasis was an incidental finding. The subject had a milder such event after 1.5 months of therapy, and that resolved with temporary interruption of the study medication and lansoprazole. The LIC at Week 24 was 9.7 mg Fe/g dw. The subject completed the Core protocol and continued on the Extension protocol at deferasirox up to 20 mg/kg/day without recurrence of the SAE.

2. *Subject 0801 00002* (D5 arm) had cellulitis and exacerbation of an existing leg ulcer after 6 months of treatment; this was considered a serious wound complication. Deferasirox had been escalated from 5 to 10 mg/kg/day at week 24 per protocol. The subject was treated with antibiotics and local measures. The event resolved approximately 6 months later. The subject completed both the Core and Extension protocols treated at a maximum dose of deferasirox of 10 mg/kg/day.

3. *Subject 1831 00015* (D5 arm) was hospitalized with right upper quadrant pain and jaundice after (b) (6) months of treatment with deferasirox 5 mg/kg/day. The ALT was 9x ULN, AST was

5x ULN, total bilirubin was 3.5x ULN, and alkaline phosphatase was 3.7x ULN. Study drug was discontinued, and the subject was treated symptomatically. Testing for hepatitis B and C were negative. On follow-up 14 months later, the ALT is 4x ULN, AST 1.5x ULN, total bilirubin 1.4x ULN, and alkaline phosphatase was normal. The LIC at study completion was 3.3 mg Fe/g dw. The subject did not continue onto the Extension protocol.

4. *Subject 0704_00004* (D10 arm) was hospitalized with pruritus, pyrexia, and rash after (b) (6) weeks of treatment with deferasirox 10 mg/kg/day. Study drug was interrupted, and the symptoms were resolved 4 weeks later. Study drug was re-initiated at 5 mg/kg/day. The pruritus and rash recurred in one day. Study drug was discontinued permanently, and the subject was withdrawn from the study.

5. *Subject 0801_00004* (D10 arm) had several episodes of upper abdominal pain starting day (b) (6) of treatment with deferasirox 10 mg/kg/day. Study drug was escalated at Week 24 to 20 mg/kg/day per protocol. After 9 months on study, he was diagnosed as having antral gastritis and a duodenal ulcer due to H. pylori. Study drug was interrupted. He was treated with symptomatic therapy and antibiotics. The event was resolved 5 months later, and deferasirox was restarted at 10 mg/kg/day on the Extension protocol. Study was interrupted again (b) (6) month later when the subject was hospitalized with abdominal pain, diarrhea and melena, which were diagnosed as chronic Helicobacter gastritis. He was treated with antibiotics again and study drug was restarted (b) (6) day later at the same dose. He completed the Extension protocol on study drug without recurrence of the event.

6. *Subject 1652_00007* (Placebo arm) crossed over from placebo to deferasirox 20 mg/kg/day in the Extension protocol. After (b) (6) months on study drug, he was hospitalized with jaundice, epigastric pain, myalgias and malaise. The ALT was 6x ULN, AST was 10.7x ULN, and a later total bilirubin was 19.7x ULN. Alkaline phosphatase was normal. Tests for hepatitis A, B and C were negative. Cholelithiasis was found but without cholecystitis. Study drug was interrupted. The hepatitis improved, and he was restarted on deferasirox 5 mg/kg/day about 3 months later. The dose was escalated back to 20 mg/kg/day over the next 4 weeks, and he completed the Extension protocol at the dose. Jaundice was on-going at the end of the study. The LIC had fallen from 22.1 to 15.1 mg Fe/g dw 6 months after starting deferasirox.

Cases 2 and 5 appear to be due to infection rather than deferasirox. The rash and pruritus in Case 4 recurred on rechallenge, and this reviewer agrees that the event was related to deferasirox. Of the three cases of hepatopathy (1, 3 and 6), two were rechallenged without recurrence, and the third is on-going with limited follow-up information. The potential for serious liver toxicity is therefore not clear.

7.3.3 Dropouts and/or Discontinuations

Thirteen subjects discontinued use of study drug prior to completion of the study due to an adverse event (Table 26). This includes subjects who discontinued drug prematurely but continued to be observed through the end of the study and completion of study procedures. Nine discontinuations occurred in the Core protocol and four (subjects 0402_00009, 0406_00002, 0801_00001 and 1831_00018) in the Extension protocol. Two discontinuations in the Core

protocol were subjects being treated with placebo; the adverse events for those subjects were optic neuritis and anemia.

Table 26: Drug Discontinuations Due to Adverse Events

Subject	Deferasirox Treatment Group[1]	Considered Drug Related	Preferred Term
0401_00003	5 mg/kg	No	Pelvic fracture
0402_00009	5 mg/kg	No	Anaemia, portal vein thrombosis
0405_00002	5 mg/kg	Yes	Anaemia
1103_00004	5 mg/kg	Yes	Proteinuria
1831_00015	5 mg/kg	Yes	Hepatotoxicity
0501_00002	10 mg/kg	No	Pregnancy
0704_00004	10 mg/kg	Yes	Pruritus, Rash
1831_00026	10 mg/kg	No	Pregnancy
0406_00002	Cross over	Yes	Blood bilirubin increased, creatinine renal clearance decreased
0801_00001	Cross over	No	Duodenal ulcer
1831_00018	Cross over	Yes	Rash
0401_00004	Placebo	No	Optic neuritis
0402_00001	Placebo	No	Anaemia

[1]Randomized arm in the Core protocol

The adverse events leading to drug discontinuation were considered at least possibly drug-related for six subjects. These included two subjects with rash and one each with anemia, elevated liver enzymes, proteinuria, or elevated bilirubin with decreased creatinine clearance.

Two subjects had an LIC <5 mg Fe/g dw within 3 months of the event. The LIC was 4.8 for subject 0402_00009 and 3.3 for subject 1831_00015. For the remainder of the subjects who discontinued drug early, the most recent LIC was >7 mg Fe/g dw.

7.3.4 Significant Adverse Events

Table 27 shows the incidence in the 158 subjects treated with deferasirox of the nine categories of adverse events of special interest described in Section 7.1.2.

Table 27: Adverse Events of Special Interest

Adverse Event of Special Interest	Number (%)
Increased serum creatinine	5 (3%)
Renal tubular disorders	0
Acute renal failure	5 (3%)
Increased liver transaminases	6 (4%)
Hepatic failure	2 (1%)
Hearing loss	4 (3%)
Lens opacities, retinal changes and optic neuritis	4 (3%)
Gastrointestinal haemorrhage and ulcers; oesophagitis	4 (3%)
Peripheral blood cytopenias	0

Of the five subjects with reports of acute renal failure, only one (Subject 0406_00002) had low creatinine clearance, and the remainder were proteinuria. When none of the preferred terms

listed in Table in section 7.1.2 were excluded in the search, a total of 9 (6%) of the subjects had adverse events related to renal function.

Of the two subjects with reports of hepatic failure, only one (Subject 1831_00015) had liver toxicity; the other subject had liver lesions and adenopathy on ultrasound. An additional search revealed 16 (10%) subjects with adverse events fulfilling the SMQs Hepatic disorders, Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions, or Liver related investigations, signs and symptoms.

Four subjects had ocular events of interest, including one subject (Subject 1103_00004) with retinal detachment after 11 months on study, and three subjects with cataracts. Only one event was considered more than mild (Subject 1831_00031 with worsening cataract). The subject had a history of cataracts at study entry and was hospitalized for surgical therapy after one day of treatment with deferasirox. Study drug administration for that subject was not altered by the event.

Sixteen subjects (10%) had anemia or worsening anemia reported, but there were no adverse events related to other cytopenias. Of the reports of hearing loss, two were mild and two were moderate; only one (Subject 1831_00007) was considered drug related.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

An adverse event was reported by 83% of the subjects treated with deferasirox and 80% of those treated with placebo. The numbers of subjects with adverse events by SOC in decreasing order of incidence in all treated subjects are shown in Table 28. The SOCs with at least a 5% difference between all treated subjects and those on placebo are general disorders and administration site conditions (34% vs 23%), blood and lymphatic system disorders (13% vs 4%), reproductive system and breast disorders (8% vs 0%), skin and subcutaneous tissue disorders (16% vs 9%), infections and infestations (54% vs 48%), eye disorders (9% vs 4%), and renal and urinary disorders (7% vs 2%).

Table 28: Adverse Events by SOC For Study A2209

	Up to 2 Years Follow-up				Up to 1 Year Follow-up					
	Deferasirox[1] 5 mg/kg/day (n=55)		Deferasirox[1] 10 mg/kg/day (n=55)		Cross Overs (n=48)		Placebo[1] (n=56)		All Treated (n=158)	
System Organ Class	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Infections and infestations	30	55	32	58	23	48	27	48	85	54
Gastrointestinal disorders	20	36	29	53	18	38	24	43	67	42
General disorders and administration site conditions	21	38	17	31	16	33	13	23	54	34
Nervous system disorders	11	20	14	25	8	17	10	18	33	21
Musculoskeletal and connective tissue disorders	13	24	10	18	9	19	12	21	32	20
Respiratory, thoracic and mediastinal disorders	12	22	12	22	7	15	9	16	31	20

Table 28: Adverse Events by SOC For Study A2209

	Up to 2 Years Follow-up				Up to 1 Year Follow-up					
	Deferasirox[1] 5 mg/kg/day (n=55)		Deferasirox[1] 10 mg/kg/day (n=55)		Cross Overs (n=48)		Placebo[1] (n=56)		All Treated (n=158)	
System Organ Class	n	%	n	%	n	%	n	%	n	%
Skin and subcutaneous tissue disorders	10	18	11	20	5	10	5	9	26	16
Investigations	8	15	9	16	6	13	7	13	23	15
Blood and lymphatic system disorders	7	13	9	16	4	8	2	4	20	13
Injury, poisoning and procedural complications	9	16	6	11	0	0	5	9	15	9
Eye disorders	6	11	4	7	4	8	2	4	14	9
Reproductive system and breast disorders	3	5	8	15	2	4	0	0	13	8
Renal and urinary disorders	4	7	6	11	1	2	1	2	11	7
Cardiac disorders	3	5	4	7	3	6	4	7	10	6
Hepatobiliary disorders	2	4	5	9	3	6	1	2	10	6
Psychiatric disorders	3	5	4	7	2	4	4	7	9	6
Ear and labyrinth disorders	3	5	3	5	2	4	2	4	8	5
Metabolism and nutrition disorders	4	7	2	4	2	4	4	7	8	5
Vascular disorders	2	4	1	2	1	2	3	5	4	3
Immune system disorders	2	4	1	2	0	0	0	0	3	2
Pregnancy, puerperium and perinatal conditions	1	2	2	4	0	0	0	0	3	2
Congenital, familial and genetic disorders	1	2	0	0	1	2	0	0	2	1
Endocrine disorders	0	0	0	0	2	4	1	2	2	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	2	0	0	1	2	0	0	2	1
Social circumstances	0	0	1	2	0	0	0	0	1	1
Surgical and medical procedures	0	0	0	0	0	0	1	2	0	0

[1]Randomized arm in the Core protocol

The adverse events by PT occurring in at least 5% of the subjects treated with deferasirox are shown in Table 29. The preferred terms for adverse events occurring in at least 10% of treated subject are pyrexia, upper respiratory tract infection, diarrhea, headache, abdominal pain upper, nausea, abdominal pain, and anemia. The preferred terms with at least 5% difference between the treated subjects and the placebo group included abdominal pain upper (13% vs 0%), anemia (10% vs 4%), gastroenteritis (9% vs 4%), and influenza (9% vs 2%).

The relatively high incidence of abdominal pain raised a concern that was explored further. On the SMQ analysis of the adverse events for the subjects treated with active drug, 46 (29%) fulfilled SMQ for acute pancreatitis; 16 (10%) subjects had events that were considered related, and 9 (6%) subjects' events were graded as severe. Laboratory testing did not include amylase or lipase, so the diagnosis of acute pancreatitis could not be confirmed. By comparison, an SMQ for acute pancreatitis was identified for 12 (21%) subjects on placebo.

Table 29: Common Adverse Events For Study A2209

	Up to 2 Years Follow-up				Up to 1 Year Follow-up					
	Deferasirox[1] 5 mg/kg/day (n=55)		Deferasirox[1] 10 mg/kg/day (n=55)		Cross Overs (n=48)		Placebo[1] (n=56)		All Treated (n=158)	
Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any Event	**47**	**85**	**45**	**82**	**39**	**81**	**45**	**80**	**131**	**83**
Pyrexia	11	20	8	15	8	17	8	14	27	17
Upper respiratory tract infection	8	15	12	22	7	15	11	20	27	17
Diarrhoea	8	15	7	13	9	19	6	11	24	15
Headache	3	5	11	20	7	15	8	14	21	13
Abdominal pain upper	4	7	9	16	7	15	0	0	20	13
Nausea	5	9	9	16	5	10	7	13	19	12
Abdominal pain	5	9	7	13	6	13	4	7	18	11
Anaemia	7	13	6	11	3	6	2	4	16	10
Gastroenteritis	4	7	8	15	3	6	2	4	15	9
Influenza	4	7	7	13	4	8	1	2	15	9
Nasopharyngitis	6	11	5	9	2	4	5	9	13	8
Cough	3	5	4	7	5	10	4	7	12	8
Fatigue	3	5	6	11	3	6	4	7	12	8
Vomiting	4	7	3	5	5	10	4	7	12	8
Oropharyngeal pain	4	7	7	13	1	2	2	4	12	8
Rash	3	5	6	11	2	4	3	5	11	7
Tonsillitis	5	9	2	4	4	8	2	4	11	7
Rhinitis	2	4	6	11	2	4	1	2	10	6
Pharyngitis	6	11	2	4			2	4	8	5

[1]Randomized arm in the Core protocol

An adverse event graded as severe was reported by 20% of the subjects treated with deferasirox and 16% of those in the placebo group. Severe adverse events that occurred in at least 2% of treated subjects are listed in Table 30. Severe abdominal pain or gastroenteritis occurred in 4% of the treated subject but in none of those in the placebo group.

Table 30: Severe Adverse Events For Study A2209

	Up to 2 Years Follow-up				Up to 1 Year Follow-up					
	Deferasirox[1] 5 mg/kg/day (n=55)		Deferasirox[1] 10 mg/kg/day (n=55)		Cross Overs (n=48)		Placebo[1] (n=56)		All Treated (n=158)	
Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any Severe Event	**10**	**18**	**12**	**22**	**9**	**19**	**9**	**16**	**31**	**20**
Abdominal pain	4	7	2	4	1	2			7	4
Anaemia	2	4	2	4	3	6	1	2	7	4
Gastroenteritis	1	2	4	7	1	2			6	4
Pyrexia			3	5					3	2

[1]Randomized arm in the Core protocol

An adverse event suspected to be related to study drug was reported by 30% of the subjects treated with deferasirox and 16% of those in the placebo group. Suspected adverse events that

occurred in at least 2% of treated subjects are listed in Table 31. The preferred terms with at least 4% difference between the treated subjects and the placebo group included diarrhea (7% vs 2%), rash (6% vs 2%), and abdominal pain upper (4% vs 0%). Additionally, all reports of the adverse event blood creatinine increased suspected to be related to study drug occurred in subjects treated with deferasirox (3% vs 0%).

Table 31: Suspected Adverse Events For Study A2209

	Up to 2 Years Follow-up				Up to 1 Year Follow-up					
	Deferasirox[1] 5 mg/kg/day (n=55)		Deferasirox[1] 10 mg/kg/day (n=55)		Cross Overs (n=48)		Placebo[1] (n=56)		All Treated (n=158)	
Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any Suspected Event	**14**	**25**	**21**	**38**	**12**	**25**	**9**	**16**	**47**	**30**
Diarrhoea	1	2	6	11	4	8	1	2	11	7
Rash	2	4	5	9	2	4	1	2	9	6
Nausea	3	5	4	7	1	2	4	7	8	5
Abdominal pain upper	3	5	1	2	2	4			6	4
Abdominal pain	3	5	1	2	1	2	1	2	5	3
Blood creatinine increased			3	5	2	4			5	3
Headache	2	4	1	2	1	2	2	4	4	3
Vomiting	1	2	1	2	1	2	1	2	3	2

[1]Randomized arm in the Core protocol

7.4.2 Laboratory Findings

Laboratory testing was performed at screening visits for the Core protocol and then at every 4-weekly study visit and at end of study in the Core and Extension protocols. The applicant noted that in the Core protocol, the laboratory tests noted to vary with dose and/or over time were creatinine, creatinine clearance and AST. In the 120-day update, the applicant indicated that the changes in laboratory values in the Extension protocol were similar to those in the Core protocol.

7.4.2.1 Critical Laboratory Test Results

Extreme outliers in hematopoietic, hepatic and renal testing were identified as critical laboratory test results for evaluation. Affected subjects were identified on the basis of any single abnormal test result as indicated (by comparison, the applicant's analysis required confirmed abnormalities for renal tests). The results are shown in Table 32. Some subjects were noted to have abnormal test results at baseline with the abnormality continuing through treatment, so the data are displayed both as all subjects with an abnormal test result at any time and as those subjects with the abnormality arising only after start of study drug (treatment-emergent). The only critical laboratory test results with substantial differences between the subjects treated with active drug and those on placebo were creatinine more than 133% of baseline (42% vs 13%) and elevated urine protein-to-creatinine ratio (6% vs 0%).

Table 32: Critical Laboratory Test Results

	At Any Time				Treatment-Emergent			
	All Treated (n=158)		Placebo[1] (n=56)		All Treated (n=158)		Placebo[1] (n=56)	
Result	n	%	n	%	n	%	n	%
Platelets <100,000/uL	6	4	7	13	2	1	6	11
Neutrophils < 1500/uL	10	6	4	7	10	6	4	7
ALT >5x ULN	2	1	1	2	2	1	1	2
AST >5x ULN	3	2	1	2	3	2	1	2
Creatinine >133% Baseline	69	44	7	13	66	42	7	13
Creatinine >1x ULN	10	6	2	4	10	6	2	4
Creatinine Clearance <60 mL/min	4	3	1	2	4	3	1	2
Urine Protein/Creatinine >1 mg/mg	9	6	0	0	9	6	0	0

7.4.2.2 Trends in Laboratory Test Results Over Time

This reviewer conducted repeated measures analyses on the laboratory values from scheduled study visits and end of study. Visits through Visit 19 or end of phase (the Core protocol visits) were used to assess differences between treatment arms. For subjects from the active treatment arms in the Core protocol, visits from screening through Visit 31 or end of study (the Core and Extension protocol visits), were used to assess differences in the treated subjects over time. The following laboratory tests were evaluated:

- Hematology (WBC, ANC, platelet count, hemoglobin)
- Liver (alkaline phosphatase, GGT, AST, ALT, total bilirubin)
- Renal (creatinine, creatinine clearance, urine protein, urine protein creatinine ratio)
- Other Chemistries (albumin, calcium, glucose, potassium)

The repeated measures analysis confirmed that there were no significant differences between treatment arms in the Core protocol for any of the laboratory tests (F=0.03-1.89, p-values=0.12-0.97).

To determine if there were any longer-term trends (up to 2 years of follow-up) in laboratory test results, paired data from screening and end of study were identified for subjects on the D5 and D10 arm who were treated on the Extension protocol. Only subjects who had completed the end of study visit were included in the analysis. The results are shown in Table 33. There were significant reductions in alkaline phosphatase, GGT, ALT and AST, consistent with the treatment effect of reduction in liver iron burden. However, there were also significant reductions in creatinine clearance (p<0.0001) and calcium (p=0.02), and an increase in serum creatinine (<0.0001). In addition, there was a trend for a reduction in hemoglobin (p=0.09).

Table 33: Laboratory Test Results Over Time

Laboratory Test	n	Screening	End of Study	p-value
White Blood Cells (10^9/L)	59	11.7 (9.6-13.7)*	11.0 (9.4-12.7)	0.28
Neutrophils (10^9/L)	40	4.8 (4.1-5.5)	4.5 (3.8-5.3)	0.43
Platelets (10^9/L)	59	454 (370-538)	463 (374-551)	0.89
Hemoglobin (g/L)	60	82 (76-88)	76 (71-81)	0.09

Table 33: Laboratory Test Results Over Time

Laboratory Test	n	Screening	End of Study	p-value
Alkaline Phosphatase (U/L)	60	84 (76-94)	78 (68-89)	0.02
GGT (U/L)	61	25 (19-31)	18 (15-21)	0.006
ALT (U/L)	59	34 (28-40)	18 (16-21)	<0.0001
AST (U/L)	60	39 (34-44)	28 (24-32)	<0.0001
Total Bilirubin (umol/L)	61	58 (51-65)	60 (52-68)	0.30
Creatinine (umol/L)	59	49 (46-53)	56 (51-60)	<0.0001
Creatinine Clearance (mL/min)	52	138 (127-149)	120 (112-129)	<0.0001
Urine Protein (mg/L)	61	189 (143-234)	182 (142-221)	0.75
Protein Creatinine Ratio (mg/mg)	61	0.24 (0.21-0.28))	0.26 (0.22-0.29)	0.41
Albumin (g/L)	60	47 (46-47)	47 (46-47)	0.96
Calcium (mmol/L)	61	2.29 (2.27-2.33)	2.27 (2.24-2.30)	0.02
Glucose (mmol/L)	61	4.55 (4.29-4.82)	4.52 (4.29-4.75)	0.79
Potassium (mmol/L)	61	4.31 (4.21-4.42)	4.27 (4.18-4.36)	0.33

* Mean (95% confidence interval)

7.4.3 Vital Signs

In the Core and Extension protocols, vital signs were to be assessed at each visit and at end of study. The applicant reported that there were no differences in vital signs between treatment groups or relevant changes from baseline.

This reviewer compared the effect of treatment arm on vital signs using a repeated measures analysis. Only data from scheduled visits through the end of the Core protocol were included in the analyses. There were no differences across treatment arms found in weight, systolic blood pressure, diastolic blood pressure or heart rate (F=0.08-0.94, p-values=0.39-0.92). There were also no differences across time for any of the vital signs through the end of the Extension protocol for subjects on the active treatment arms with up to two years of follow-up (F=0.23-0.68, p-values=0.84-0.99).

This reviewer also sought to determine if there were differences between treatment arms in the proportion of subjects with critical levels of vital signs. For this analysis, each subject was scored as having or not having experienced the target outcome through the end of the Core protocol. The results are shown in Table 34. There were no significant differences across treatment arms. It was noted that there was a relatively high proportion of subjects with systolic blood pressure <90. This may have been due to the inclusion of pediatric subjects for whom it would be normal to have a systolic blood pressure <90.

Table 34: Critical Vital Signs in Study A2209 Core

Vital Sign	Deferasirox 5 mg/kg/day	Deferasirox 10 mg/kg/day	Placebo
Systolic Blood Pressure >150	3 (5%)[1]	3 (5%)	1 (2%)
Diastolic Blood Pressure >90	2 (4%)	1 (2%)	2 (4%)
Heart rate >120	2 (4%)	2 (4%)	1 (2%)
Heart rate <50	0	1 (2%)	0
Systolic Blood Pressure <90	8 (15%)	7 (13%)	8 (14%)

[1] Number (%) of subjects

There was one subject identified with extensive weight loss. Subject 1653_00011 was receiving deferasirox at 5 mg/kg/day. She experienced 8% weight loss from baseline following surgery for correction of an atrial septal defect. No additional information was provided.

7.4.4 Electrocardiograms (ECGs)

In the Core protocol, an ECG was performed at screening and at end of study. In the Extension protocol, an ECG was performed at the end of study. The data file provided an interpretation of the ECG as normal, clinically insignificant abnormality or clinically significant abnormality. The specific abnormality was identified only for those listed as clinically significant.

The sponsor reported that at screening, 161 subjects had an ECG; 70% were normal, 28% had an insignificant abnormality, and 2% had a clinically significant abnormality. Throughout the Core and Extension protocols, the most extreme result for the post treatment ECGs was normal for 59% of the subjects, clinically insignificant abnormality for 39%, and clinically significant abnormality for 3%.

In order to determine if ECG changes vary by time on study, this reviewer sought the incidence of abnormalities by the end of each protocol. At the end of the Core protocol, 43 subjects on the placebo arm and 86 on active drug had an ECG. For the placebo group, the results were normal in 79%, clinically insignificant for 19% and clinically significant for 2%; the distribution was skewed toward more abnormalities for the subjects treated with deferasirox (63%, 34% and 3%, respectively). There were 90 subjects with an ECG for the end of the Extension protocol; this group had a slightly higher incidence of clinically insignificant abnormalities (57% normal, 42% clinically insignificant, and 1% clinically significant). The applicant clarified that the nature of the clinically insignificant abnormalities was not available, since only the general interpretation was recorded in the Case Report Form.

Three subjects had clinically significant ECG abnormalities during the Core protocol that were not present at screening.

- Subject 0401_00007 was a 69 year old male treated with deferasirox 10 mg/kg. The baseline LIC was 15.7 mg Fe/g dw. The medical history included diabetes mellitus and glaucoma. This subject also had a reduction in the creatinine clearance from 83 to 62 mL/min during the Core protocol. LIC on Day 266 was 3.7 mg Fe/g dw. On study Day (b) (6), the subject presented with exertional dyspnea and was found to have *atrial fibrillation* on ECG. Diuretics and subsequently ramipril were administered, the event was on-going at the time of last follow-up. Study drug was interrupted at diagnosis of atrial fibrillation and restarted at the same dose on Day 393. The subject completed the Core protocol and was continued on deferasirox 10 mg/kg in the Extension study. He was taken off study drug Day 510 when the LIC was 1.4 mg Fe/g dw. The event was on-going at the end of study. The investigator did not consider the atrial fibrillation to be related to deferasirox.

- Subject 1101_00007 was an 11 year old male treated with deferasirox 5 mg/kg. The baseline LIC was 9.5 mg Fe/g dw. *Left ventricular hypertrophy* was found on ECG at the end of the

Core protocol when the LIC was 6 mg Fe/g dw. The ECG finding was considered unrelated to study drug by the investigator. The subject was continued on the Extension protocol at 10 mg/kg deferasirox. There are no additional ECGs thereafter.

- Subject 1103_00004 was a 24 year old male treated with deferasirox 5 mg/kg. The baseline LIC was 11.7 mg Fe/g dw. The deferasirox dose was increased to 10 mg/kg at week 24 per protocol. Nonspecific *intraventricular conduction delay* was found on ECG at the end of the Core protocol when the LIC was 15 mg Fe/g dw. The ECG finding was considered unrelated to study drug by the investigator. The subject did not continue on the Extension protocol.

The adverse event data file was also searched by HLGT Cardiac Arrhythmias (10007521) and HLT ECG Investigations. These searches yielded four additional cases. One subject treated with deferasirox 10 mg/kg was reported to have *tachyarrhythmia* without further information. The other three subjects (paroxysmal tachycardia, sinus tachycardia and bigeminy) were being treated with placebo.

Reviewer Comment: The results suggest there is no increased risk of clinically important cardiac arrhythmias with use of deferasirox, although it is not clear whether the clinically insignificant but unspecified abnormalities that increased in proportion over time portend more significant cardiac issues that might arise with longer use of deferasirox.

7.4.5 Special Safety Studies/Clinical Trials

In the Core protocol, auditory testing, ocular examination and an echocardiogram, were performed at screening and at end of study. In the Extension protocol, auditory testing, ocular examination and an echocardiogram were performed at the end of study.

7.4.5.1 Auditory Testing

At the end of the Core protocol, 46 subjects on the placebo arm and 84 on active drug had auditory testing. For the placebo group, the results were normal in 70%, clinically insignificant for 24% and clinically significant for 7%; the distribution of results by category was similar for the subjects treated with deferasirox (67%, 26% and 7%, respectively). There were 88 subjects with an auditory exam for the end of the Extension protocol; this group had a slightly higher incidence of clinically insignificant abnormalities (59% normal, 34% clinically insignificant, and 7% clinically significant). The clinically insignificant abnormalities were not identified.

Two subjects treated with deferasirox had clinically significant abnormalities on auditory testing that were not present at screening or that worsened in comparison to screening:

- Subject 1831_00024 on 10 mg/kg/day deferasirox had new but mild sensorineural hearing loss on the right.

- Subject 0801_00003 on 10 mg/kg/day deferasirox had worsening of pre-existing hearing loss in the left ear to a grade of moderate.

The adverse event data file was also searched by the SOC Ear and labyrinth disorders. Six subjects were identified as having tinnitus or hearing loss. Five were subjects treated with deferasirox; 3 had mild symptoms, and two had moderate hypoacusis. The sixth subject, treated with placebo, had mile neurosensory hearing loss. Drug was not interrupted for any of the events.

7.4.5.2 Ocular Examinations

At the end of the Core protocol, 45 subjects on placebo and 87 on active drug had ocular exams. For the placebo group, the results were normal in 60%, clinically insignificant for 33% and clinically significant for 3%; the distribution of results by category showed fewer subjects with abnormalities among those treated with deferasirox (68%, 31% and 1%, respectively). There were 90 subjects with an ocular exam for the end of the Extension protocol; there was no substantial difference in the distribution of results by category (72% normal, 26% clinically insignificant, and 2% clinically significant). The clinically insignificant abnormalities were not identified.

Two subjects treated with deferasirox had had new clinically significant abnormalities on ocular exam after treatment:

- Subject 1244_00004 on 5 mg/kg/day deferasirox had advancement of a cataract that was considered severe at the end of Core protocol study visit.

- Subject 1831_00029 on 5 mg/kg/day deferasirox had mild cataracts bilaterally noted at the end of Extension protocol study visit.

The adverse event data file was also searched by the SOC Eye disorders. Thirteen subjects treated with deferasirox were identified as having events ocular disorders, including 5 conjunctivitis, 3 cataracts, 2 with dry eyes, 1 retinal detachment, 1 strabismus and 1 reduced visual acuity All were mild except for one cataract (severe). Three were suspected to be related to deferasirox (two cataracts and one conjunctivitis, but there were no drug interruptions due to the ocular events.

7.4.5.3 Echocardiograms

Results of the echocardiograms were not provided in the application. The applicant clarified that any significant abnormalities on an echocardiogram would be entered as an adverse event. A search of the adverse event file showed no events that pertained to abnormal echocardiograms, although this search would not include events identified as the abnormality found (e.g., tricuspid regurgitation) without reference to the test itself.

7.4.6 Immunogenicity

No additional information addressing immunogenicity was submitted in this supplement.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

An adverse event profile by actual deferasirox dose was sought. For each adverse event, the actual dose of deferasirox was identified. Adverse events were grouped by actual dose as 5 mg/kg (median 5, range 1.4-7.3), 10 mg/kg (median 10, actual 7.5-14.9), 20 mg/kg (median 20, range 15.2-39.8) and summarized in Table 35. Only the 158 subjects treated with deferasirox were included. The results should be interpreted with caution, since subjects who interrupted drug use before reporting the adverse event are listed as a dose of 0 and are not included in the tabulation, so some events may be missing. Nonetheless, headache, diarrhea and abdominal pain appear to occur more frequently at the higher doses of deferasirox. Additionally, all instances of blood creatinine increased, gastroenteritis, insomnia and fatigue occurred in subjects taking deferasirox at 10 or 20 mg/kg.

Table 35: Adverse Events by Actual Dose Group

	Actual Deferasirox Dose on Day of Event[1]					
	5 mg/kg (n=77)		10 mg/kg (n=130)		20 mg/kg (n=80)	
Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**
Any Event	**40**	**52**	**89**	**68**	**54**	**68**
Upper respiratory tract infection	6	8	11	8	11	14
Headache	2	3	15	12	8	10
Diarrhea	4	5	12	9	8	10
Abdominal pain upper	4	5	7	5	8	10
Cough	3	4	2	2	6	8
Pyrexia	6	8	11	8	5	6
Nausea	4	5	9	7	5	6
Abdominal pain	2	3	6	5	5	6
Tonsillitis	4	5	3	2	5	6
Food poisoning	0	0	2	2	4	5
Pharyngitis	2	3	2	2	4	5
Anemia	2	3	9	7	3	4
Influenza	2	3	5	4	3	4
Rhinitis	1	1	5	4	3	4
Blood creatinine increased	0	0	3	2	3	4
Gastroenteritis	0	0	3	2	3	4
Insomnia	0	0	3	2	3	4
Fatigue	0	0	9	7	2	3
Nasopharyngitis	5	6	9	7	2	3
Rash	3	4	9	7	2	3
Vomiting	2	3	6	5	2	3
Arthralgia	2	3	3	2	2	3
Pain in extremity	0	0	2	2	2	3
Rhinorrhea	0	0	1	1	2	3
Hypoacusis	1	1	1	1	2	3

[1]Group by actual dose indicated as 5 mg/kg (median 5, range 1.4-7.3), 10 mg/kg (median 10, actual 7.5-14.9), 20 mg/kg (median 20, range 15.2-39.8)

7.5.2 Time Dependency for Adverse Events

Since the protocol prespecified dose modifications for efficacy every six months, the duration of follow-up on any particular dose is relatively short. Moreover, given that NTDT patients would be expected to use this drug life-long, the 2-year follow-up of the study participants would not provide adequate safety information about long-term use. Hence, a meaningful analysis of the time dependency of the adverse events could not be performed with the data available.

7.5.3 Drug-Demographic Interactions

Table 36 lists the adverse events in the treated subjects by gender in decreasing order of the difference in incidence between genders. Only adverse events with a difference in incidence of at least 3% are shown. Anemia and arthralgia predominated in females, while increased blood creatinine and gastrointestinal events, such as abdominal pain, vomiting, gastritis and diarrhea, predominated in males.

Table 36: Adverse Events By Gender

	Females (n=74)		Males (n=84)	
Preferred Term	**n**	**%**	**n**	**%**
Anemia	11	15	5	6
Influenza	4	5	11	13
Nausea	6	8	13	15
Tonsillitis	8	11	3	4
Arthralgia	6	8	1	1
Pyrexia	10	14	17	20
Upper respiratory tract infection	10	14	17	20
Abdominal pain	6	8	12	14
Blood creatinine increased	0	0	5	6
Rhinorrhea	0	0	4	5
Pharyngitis	2	3	6	7
Vomiting	4	5	8	10
Dysmenorrhea	3	4	0	0
Eczema	3	4	0	0
Menstrual disorder	3	4	0	0
Pregnancy	3	4	0	0
Abdominal tenderness	0	0	3	4
Influenza like illness	0	0	3	4
Jaundice	0	0	3	4
Melena	0	0	3	4
Paresthesia	0	0	3	4
Respiratory tract infection	0	0	3	4
Sinusitis	0	0	3	4
Cough	7	9	5	6
Gastritis	1	1	4	5
Diarrhea	10	14	14	17

Table 37 lists the adverse events in the treated subjects by race in decreasing order of the difference in incidence between Caucasians and Asians. There were too few subjects of other races for meaningful comparison. Only adverse events with a difference in incidence of at least 3% are shown. Gastrointestinal events and increased blood creatinine predominated in Caucasians.

Table 37: Adverse Events By Race

	Caucasian (n=87)		Asian (n=68)		Other (n=3)	
Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**
Diarrhea	19	22	3	4	2	67
Nausea	16	18	1	1	2	67
Abdominal pain upper	17	20	3	4	0	0
Headache	17	20	4	6	0	0
Abdominal pain	15	17	3	4	0	0
Tonsillitis	11	13	0	0	0	0
Nasopharyngitis	12	14	1	1	0	0
Vomiting	9	10	1	1	2	67
Influenza	11	13	3	4	1	33
Pyrexia	18	21	9	13	0	0
Food poisoning	0	0	5	7	1	33
Asthenia	6	7	0	0	0	0
Rhinitis	8	9	2	3	0	0
Cough	9	10	3	4	0	0
Oropharyngeal pain	9	10	3	4	0	0
Pain in extremity	5	6	0	0	0	0
Urinary tract infection	5	6	0	0	0	0
Gastroenteritis	10	11	4	6	1	33
Arthralgia	6	7	1	1	0	0
Upper respiratory tract infection	12	14	13	19	2	67
Fatigue	8	9	3	4	1	33
Gastritis	1	1	4	6	0	0
Edema peripheral	4	5	0	0	0	0
Tinnitus	4	5	0	0	0	0
Eczema	0	0	3	4	0	0
Pharyngitis	3	3	5	7	0	0
Dyspepsia	2	2	4	6	0	0
Abdominal distension	3	3	0	0	0	0
Cataract	3	3	0	0	0	0
Dysmenorrhea	3	3	0	0	0	0
Hypoacusis	3	3	0	0	0	0
Menstrual disorder	3	3	0	0	0	0
Muscle spasms	3	3	0	0	0	0
Pruritus	3	3	0	0	0	0
Sinusitis	3	3	0	0	0	0
Skin ulcer	3	3	0	0	0	0
Syncope	3	3	0	0	0	0
Bronchitis	1	1	3	4	0	0
Blood creatinine increased	4	5	1	1	0	0

Table 38 lists the adverse events in the treated subjects by age in decreasing order of the difference in incidence between age groups with children being those subjects less than 17 years old at enrollment. Only adverse events with a difference in incidence of at least 3% are shown. Gastrointestinal events, increased blood creatinine, fatigue and arthralgias predominated in adults, while the incidences of elevated alanine aminotransferase, gastritis and upper limb fractures were higher in children. There was only one subject at least 65 years of age (Subject 0401_00007), and this subject is included in the adult age group. Adverse events listed for this subject include atrial fibrillation, dysphonia, pyrexia, herpes zoster, dry mouth, pharyngitis, blood creatinine increased, and vertigo.

Table 38: Adverse Events By Age Group

	Children (n=16)		Adults (n=142)	
	n	%	n	%
Abdominal pain upper	0	0	20	14
Abdominal pain	0	0	18	13
Upper limb fracture	2	13	0	0
Alanine aminotransferase increased	2	13	2	1
Gastroenteritis	0	0	15	11
Gastritis	2	13	3	2
Diarrhea	1	6	23	16
Food poisoning	2	13	4	3
Fatigue	0	0	12	8
Oropharyngeal pain	0	0	12	8
Vomiting	0	0	12	8
Pharyngitis	2	13	6	4
Adrenal insufficiency	1	6	0	0
Amenorrhea	1	6	0	0
Diarrhea infectious	1	6	0	0
Electrocardiogram T wave inversion	1	6	0	0
Fungal infection	1	6	0	0
Hemolysis	1	6	0	0
Left ventricular hypertrophy	1	6	0	0
Lower limb fracture	1	6	0	0
Osteopenia	1	6	0	0
Pneumonia	1	6	0	0
Post streptococcal glomerulonephritis	1	6	0	0
Rash papular	1	6	0	0
Road traffic accident	1	6	0	0
Tooth abscess	1	6	0	0
Rash	2	13	9	6
Acute tonsillitis	1	6	1	1
Chest pain	1	6	1	1
Rhinitis allergic	1	6	1	1
Arthralgia	0	0	7	5
Eczema	1	6	2	1
Gastroenteritis viral	1	6	2	1

Table 38: Adverse Events By Age Group

	Children (n=16)		Adults (n=142)	
	n	%	n	%
Respiratory tract infection	1	6	2	1
Viral infection	1	6	2	1
Nasopharyngitis	2	13	11	8
Dyspepsia	0	0	6	4
Insomnia	0	0	6	4
Conjunctivitis	1	6	3	2
Dizziness	1	6	3	2
Influenza	1	6	14	10
Blood creatinine increased	0	0	5	4
Urinary tract infection	0	0	5	4
Pain in extremity	1	6	4	3

An additional analysis was performed to determine if the change in creatinine was age-related. There were six children with follow-up through end of study. The difference in creatinine between screening and end of study was not significant for these children, and the mean difference (+2.3 umol/L) was higher than that for the adults (+7.1 umol/L). The significance of the difference in creatinine from screening to baseline as described in Section 7.4.2.2 thus appeared to be driven by the adult subjects.

7.5.4 Drug-Disease Interactions

Table 39 lists the adverse events in the treated subjects by type of thalassemia in decreasing order of the incidence in subjects with thalassemia intermedia. Adverse events with an incidence of at least 5% in any group are shown. Gastrointestinal events and headache predominated in subjects with thalassemia intermedia.

Table 39: Adverse Events By Diagnosis

	Hgb E Beta Thalassemia (n=21)		Alpha Thalassemia (n=49)		Thalassemia Intermedia (n=88)	
Preferred Term	n	%	n	%	n	%
Diarrhea	1	5	2	4	21	24
Nausea	0	0	1	2	18	20
Pyrexia	3	14	6	12	18	20
Abdominal pain upper	1	5	3	6	16	18
Headache	2	10	3	6	16	18
Abdominal pain	1	5	2	4	15	17
Upper respiratory tract infection	4	19	10	20	13	15
Gastroenteritis	1	5	2	4	12	14
Nasopharyngitis	0	0	1	2	12	14
Influenza	2	10	2	4	11	13
Tonsillitis	0	0	0	0	11	13
Vomiting	1	5	0	0	11	13
Anemia	1	5	5	10	10	11
Fatigue	1	5	2	4	9	10

Table 39: Adverse Events By Diagnosis

	Hgb E Beta Thalassemia (n=21)		Alpha Thalassemia (n=49)		Thalassemia Intermedia (n=88)	
Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**
Oropharyngeal pain	2	10	1	2	9	10
Cough	4	19	1	2	7	8
Rash	1	5	3	6	7	8
Asthenia	0	0	0	0	6	7
Rhinitis	2	10	2	4	6	7
Arthralgia	1	5	1	2	5	6
Insomnia	0	0	1	2	5	6
Pain in extremity	0	0	0	0	5	6
Urinary tract infection	0	0	0	0	5	6
Pharyngitis	0	0	5	10	3	3
Dyspepsia	1	5	4	8	1	1
Food poisoning	1	5	4	8	1	1
Gastritis	0	0	4	8	1	1
Palpitations	2	10	0	0	1	1
Eczema	0	0	3	6	0	0
Musculoskeletal chest pain	2	10	0	0	0	0

Table 40 lists the adverse events in the treated subjects by prior transfusion history in decreasing order of the difference in incidence between those with any prior transfusions prior to study entry vs those who were untransfused. Adverse events with a difference in incidence of at least 5% are shown. Influenza-like illness, elevated GGT and cutaneous events predominated in the subjects with no prior transfusion, and anemia predominated in those who had received transfusions prior to study entry.

Table 40: Adverse Events By History of Prior Transfusions

	No Prior Trnasfusions (n=19)		Any Transfusions Prior to Study Entry (n=139)	
	n	**%**	**n**	**%**
Influenza like illness	3	16	0	0
Anemia	0	0	16	12
Dermatitis contact	2	11	0	0
Gamma-glutamyltransferase increased	2	11	0	0
Rash	3	16	8	6
Skin ulcer	2	11	1	1
Cough	0	0	12	9
Urinary tract infection	2	11	3	2
Tonsillitis	0	0	11	8
Upper respiratory tract infection	2	11	25	18
Rhinitis	0	0	10	7
Arterial disorder	1	5	0	0
Blood alkaline phosphatase increased	1	5	0	0
Bronchopneumonia	1	5	0	0
Cellulitis	1	5	0	0
Chronic sinusitis	1	5	0	0

Table 40: Adverse Events By History of Prior Transfusions

	No Prior Trnasfusions (n=19)		Any Transfusions Prior to Study Entry (n=139)	
	n	%	n	%
Creatinine renal clearance decreased	1	5	0	0
Erectile dysfunction	1	5	0	0
Flatulence	1	5	0	0
Foot fracture	1	5	0	0
Hemosiderosis	1	5	0	0
Hyperventilation	1	5	0	0
Impaired healing	1	5	0	0
Mood swings	1	5	0	0
Post procedural hemorrhage	1	5	0	0
Rib fracture	1	5	0	0
Strangury	1	5	0	0
Tachyarrhythmia	1	5	0	0
Tendon disorder	1	5	0	0
Tendonitis	1	5	0	0
Waist circumference increased	1	5	0	0
Wound complication	1	5	0	0
Xerosis	1	5	0	0
Abdominal pain	3	16	15	11

Table 41 lists the adverse events in the treated subjects by baseline LIC in decreasing order of the incidence in subjects with a baseline LIC >15 mg Fe/g dw. Gastrointestinal events and anemia occurred more frequently in those with a higher LIC at baseline.

Table 41: Adverse Events By Baseline LIC

	LIC <7 mg Fe/g dw (n=30)		LIC 7-15 mg Fe/g dw (n=72)		LIC >15 mg Fe/g dw (n=56)	
Preferred Term	n	%	n	%	n	%
Diarrhea	3	10	10	14	11	20
Pyrexia	4	13	13	18	10	18
Upper respiratory tract infection	6	20	11	15	10	18
Headache	1	3	10	14	10	18
Abdominal pain upper	3	10	7	10	10	18
Anemia	2	7	6	8	8	14
Abdominal pain	1	3	10	14	7	13
Gastroenteritis	2	7	6	8	7	13
Nausea	4	13	9	13	6	11
Influenza	1	3	8	11	6	11
Rash	2	7	3	4	6	11
Cough	1	3	6	8	5	9
Tonsillitis	2	7	4	6	5	9
Oropharyngeal pain	1	3	7	10	4	7
Vomiting	2	7	6	8	4	7
Arthralgia	0	0	3	4	4	7
Food poisoning	0	0	2	3	4	7
Fatigue	3	10	6	8	3	5

Table 41: Adverse Events By Baseline LIC

	LIC <7 mg Fe/g dw (n=30)		LIC 7-15 mg Fe/g dw (n=72)		LIC >15 mg Fe/g dw (n=56)	
Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**
Rhinitis	2	7	5	7	3	5
Pharyngitis	0	0	5	7	3	5
Dyspepsia	0	0	3	4	3	5
Insomnia	0	0	3	4	3	5
Blood creatinine increased	0	0	2	3	3	5
Urinary tract infection	0	0	2	3	3	5
Bronchitis	0	0	1	1	3	5
Abdominal discomfort	1	3	0	0	3	5
Back pain	1	3	0	0	3	5
Cataract	0	0	0	0	3	5
Dyspnea	0	0	0	0	3	5
Nasopharyngitis	3	10	8	11	2	4
Pain in extremity	2	7	1	1	2	4
Epistaxis	2	7	1	1	1	2
Proteinuria	0	0	4	6	0	0
Dizziness	2	7	2	3	0	0
Respiratory tract infection	2	7	1	1	0	0
Viral infection	2	7	1	1	0	0
Toothache	2	7	0	0	0	0

Twenty subjects achieved an LIC <3 mg Fe/g dw after start of treatment. The only adverse events that occurred in this population with an incidence >5% more than in those not achieving an LIC <3 mg Fe/g dw were rhinitis (15% vs 5%), syncope (10% vs 1%), and abdominal pain upper (20% vs 12%).

7.5.5 Drug-Drug Interactions

Table 42 lists the adverse events in the treated subjects by prior use of chelation therapy in decreasing order of the difference in incidence between those who used chelation therapy prior to study entry vs those who did not. The two subjects for whom the history for prior chelation therapy was unknown were not included in the analysis. Only adverse events with a difference in incidence of at least 3% are shown. Gastrointestinal events, headache. anemia and hearing loss predominated in subjects who used chelation therapy prior to study entry.

Table 42: Adverse Events By History of Chelation Therapy Use

	No Prior Chelation Therapy (n=114)		Used Chelation Therapy Prior to Study Entry (n=42)	
	n	**%**	**n**	**%**
Abdominal pain	6	5	12	29
Abdominal pain upper	8	7	12	29
Diarrhea	11	10	13	31
Pyrexia	14	12	13	31
Headache	11	10	10	24
Anemia	8	7	8	19

Table 42: Adverse Events By History of Chelation Therapy Use

	No Prior Chelation Therapy (n=114)		Used Chelation Therapy Prior to Study Entry (n=42)	
	n	%	n	%
Gastroenteritis	8	7	7	17
Influenza	8	7	7	17
Nausea	11	10	8	19
Fatigue	6	5	6	14
Oropharyngeal pain	6	5	6	14
Upper respiratory tract infection	22	19	5	12
Abdominal distension	0	0	3	7
Hypoacusis	0	0	3	7
Pharyngitis	8	7	0	0
Tonsillitis	6	5	5	12
Abdominal discomfort	1	1	3	7
Tinnitus	1	1	3	7
Pain in extremity	2	2	3	7
Food poisoning	6	5	0	0
Dry eye	0	0	2	5
Duodenal ulcer	0	0	2	5
Ear discomfort	0	0	2	5
Gastroesophageal reflux disease	0	0	2	5
Heart rate decreased	0	0	2	5
Menstrual discomfort	0	0	2	5
Neck pain	0	0	2	5
Ovarian cyst	0	0	2	5
Rhinitis	6	5	4	10
Abdominal tenderness	1	1	2	5
Cataract	1	1	2	5
Sinusitis	1	1	2	5
Skin ulcer	1	1	2	5
Syncope	1	1	2	5
Arthralgia	4	4	3	7
Bronchitis	4	4	0	0
Conjunctivitis	4	4	0	0
Dizziness	4	4	0	0
Rash	7	6	4	10
Back pain	2	2	2	5
Decreased appetite	2	2	2	5
Oedema peripheral	2	2	2	5
Proteinuria	2	2	2	5
Rhinorrhoea	2	2	2	5

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No additional analyses for carcinogenicity were submitted by the sponsor. The adverse event data file was searched for the SOC Neoplasms benign, malignant and unspecified. Two cases were identified.

Subject 0801_00001, originally in the placebo arm and treated with deferasirox at 20 mg/kg/day in the Extension protocol, had a "right thumb pad verruca" after 9 months on deferasirox. It was treated with Bazuka. The event was graded as mild and considered unrelated to study drug. The event was on-going at completion of study.

Subject 1831_00005 had an "erythematous mass of the left ear lobule" at 23 months on study while taking deferasirox 10 mg/kg/day. The event was graded as mild and considered unrelated to study drug. The event was on-going at completion of study.

7.6.2 Human Reproduction and Pregnancy Data

There were three pregnancies reported in Study A2209:

Subject 0501-00002 was reported to be pregnant on Day (b) (6) of study while receiving deferasirox at 10 mg/kg/day. Study drug was discontinued Day 184. The subject delivered a healthy male infant after 9 months gestation. The subject had been using an oral contraceptive.

Subject 1831-00015 was reported to be pregnant on Day (b) (6) of study while receiving deferasirox at 5 mg/kg/day The subject underwent an elective termination of the pregnancy and continued in the study. The subject had not been using an oral contraceptive.

Subject 0501-00026 was reported to be pregnant on Day (b) (6) of study while receiving deferasirox at 10 mg/kg/day. Study drug was discontinued Day 258. The subject delivered a healthy female infant after 9 months gestation. No information was available about use of contraception by this subject.

Reviewer Comment: In the opinion of this reviewer, none of the clinical information regarding these pregnancies warrants a change in the instructions for use in pregnancy or lactation, or for potential drug interactions involving oral contraceptives, provided in the current labeling.

7.6.3 Pediatrics and Assessment of Effects on Growth

The sponsor performed an analysis of safety information for subjects <18 years of age. They found that within this subgroup of 21 subjects, the number of severe AEs was comparable to that in adults, and there were fewer AEs leading to dose modification and none to treatment discontinuation. This reviewer's analysis of adverse events for children <17 years of age is discussed in Section 7.5.3 above.

No studies of the impact of deferasirox on growth were performed.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No new information on overdosage was submitted. The maximal dose of deferasirox administered in Study A2209 was 40 mg/kg. There was also no new information addressing abuse potential or addiction.

7.7 Additional Submissions / Safety Issues

7.7.1 Literature Review

Two pilot studies of deferasirox for treatment of NTDT were reviewed for safety information. There were 11 subjects in each study. Additional details of the studies are described in Section 6.1.11.

Voskaridou et al (Voskaridou, Plata 2009) reported that nausea occurred in 73% of subjects and diarrhea in 18% within the first month of treatment. None of the subjects were withdrawn due to an AE. Over the course of the 12 months of treatment, the AST and ALT declined significantly, but there were no changes in serum creatinine or 24 hour urine protein.

Ladis et al (Ladis, Berdousi 2010) reported gastrointestinal disturbances in 3 (37%) subjects, one of whom withdrew early due to the AE and noncompliance. The other two subjects experienced dizziness and malaise, but these were not severe enough to interrupt treatment. The AST and ALT were reduced significantly after 12 and 24 months of therapy. There were also significant increases in serum creatinine and reduction in creatinine clearance but only after 24 months of treatment, and but none of the subjects had a creatinine outside of the normal range.

7.7.2 Study A2202

7.7.2.1 Safety Population

The safety population for Study A2202 was comprised of 49 subjects with hereditary hemochromatosis. The group included 33 males and 16 females. The median age was 53 years (range, 19-87 years). All were caucasian. Seventeen (35%) subjects were from the US, and the remainder were from Canada or Europe. The distribution of time on study and study drug exposure at specific dose groups is shown in Table 43.

Table 43: Study A2202 - Drug Exposure

		Grouped by Actual Dose[2]		
Months	**On Study**	**5 mg/kg[2]**	**10 mg/kg[2]**	**15 mg/kg[2]**
0-3	49 (100%)[1]	23 (100%)	36 (100%)	13 (100%)
4-6	42 (86%)	13 (57%)	18 (50%)	7 (54%)
7-9	32 (65%)	9 (39%)	7 (19%)	2 (15%)
>9	26 (53%)	2 (9%)	7 (19%)	1 (8%)

[1]Number (%)
[2]Group by actual dose indicated as 5 mg/kg/day (median 5, range 2.4-7.2), 10 mg/kg/day (median 10, actual 7.6-14.9), 15 mg/kg/day (median 20, range 15.0-15.6)

7.7.2.2 Major Safety Results

There were no deaths. There was one serious adverse event report (recurrence of prostate cancer), and the event was considered unrelated to study drug. Ten subjects discontinued drug use early, and nine of the events were considered related to study drug (Table 44), including four with elevated transaminases. Five subjects experienced six events graded as severe that were considered related to study drug (diarrhea, rash, nausea, headache, vagal reaction and transaminases increased).

Table 44: Study A2202 - Drug Discontinuations Due to Adverse Events

Subject	**Considered Drug Related**	**Event**
0401_00001	No	Anxiety, impotence
0503_00002	Yes	Fever, nausea, weakness
0503_00004	Yes	Diarrhea
0508_00002	Yes	Transaminases increased
0509_00002	Yes	Diarrhea Muscle soreness
0600_00001	Yes	Impaired renal function
0600_00002	Yes	Transaminase increased
0700_00002	Yes	Skin rash
0900_00007	Yes	Transaminases increased
0900_00011	Yes	Transaminases increased

Events of special interest were identified as described in Table 22 in Section 7.1.2. Increased serum creatinine was reported for 15 (31%) subjects, increased liver transaminases for 9 (18%) subjects, hearing loss for 4 (8%) subjects, and ocular events for 4 (8%) subjects.

7.7.2.3 Common Adverse Events

An adverse event was reported for 48 (98%) of the 49 subjects. The numbers of subjects with adverse events by SOC in decreasing order of percentage are shown in Table 45.

Table 45: Study A2202 – Subjects with Adverse Events by SOC

System Organ Class	n	%
Gastrointestinal disorders	35	71
Musculoskeletal and connective tissue disorders	22	45
Infections and infestations	21	43
Investigations	20	41
General disorders and administration site conditions	16	33
Nervous system disorders	13	27
Eye disorders	10	20
Skin and subcutaneous tissue disorders	10	20
Ear and labyrinth disorders	9	18
Respiratory, thoracic and mediastinal disorders	6	12
Vascular disorders	6	12
Renal and urinary disorders	5	10
Immune system disorders	3	6
Injury, poisoning and procedural complications	3	6
Psychiatric disorders	3	6
Cardiac disorders	2	4
Reproductive system and breast disorders	2	4
Congenital, familial and genetic disorders	1	2
Hepatobiliary disorders	1	2
Neoplasms benign, malignant and unspecified	1	2

The adverse events by PT occuring in at least 5% of the subjects are shown in Table 46.

Table 46: Study A2202 – Subjects with Adverse Events by PT

Preferred Term	n	%
Diarrhoea	18	37
Blood creatinine increased	11	22
Headache	10	20
Back pain	9	18
Nausea	8	16
Abdominal pain	7	14
Alanine aminotransferase increased	7	14
Arthralgia	7	14
Fatigue	6	12
Rash	6	12
Flatulence	5	10
Nasopharyngitis	5	10
Dyspepsia	4	8
Influenza like illness	4	8

Table 46: Study A2202 – Subjects with Adverse Events by PT

Preferred Term	n	%
Renal impairment	4	8
Transaminases increased	4	8
Upper respiratory tract infection	4	8
Abdominal distension	3	6
Cough	3	6
Gastroesophageal reflux disease	3	6
Hypoacusis	3	6
Musculoskeletal pain	3	6
Vomiting	3	6

7.7.2.3 Laboratory Findings

Extreme outliers in hematopoietic, hepatic and renal testing were identified as described in Section 7.4.2. These are shown in Table 47.

Table 47: Study A2202 - Critical Laboratory Test Results

Result	n	%
Platelets <100,000/uL	0	0
Neutrophils < 1500/uL	5	10
Hgb < 1x LLN	1	2
ALT >5x ULN	3	6
AST >5x ULN	0	0
Creatinine >133% Baseline	1	2
Creatinine >1x ULN	30	80
Creatinine Clearance <60 mL/min	8	16
Urine Protein/Creatinine Ratio >1	0	0

Mild increases in serum creatinine were common (80% of subjects), but only 21 (43%) of the subjects had an elevated creatinine on more than one occasion. For the 26 subjects who completed the Extension protocol, the serum creatinine decreased significantly from baseline to end of study by paired t-test (mean 49 vs 57 umol/L, respectively, $p<0.001$). Eight subjects had a creatinine clearance less then 60 mL/min during treatment. The median actual decrease in creatinine clearance was -22 mL/min (range, -15 to -56 mL/min).

There were no Hy's Law cases. Seven (14%) subjects had ALT levels greater than 3 times the upper limit of normal, and three of these also had an AST greater than 3 times the upper limit of normal.

Only one subject had anemia (hemoglobin 129 g/L) detected during the course of the study. For the 26 subjects who completed the Extension protocol, there was no significant difference in hemoglobin from baseline to end of study by paired t-test (mean 153 vs 152 g/L, respectively, $p=0.41$).

7.7.2.3 Special Safety Studies

Four (8%) subjects had new ECG abnormalities classified as clinically significant. These included sinus arrhythmia with incomplete right bundle branch block, left ventricular hypertrophy with possible inferolateral ischemia, T wave abnormalities, and first degree heart block.

Six (12%) subjects had new clinically significant abnormalities on auditory testing, including conductive, sensorineural and combined hearing losses.

Five (10%) subjects had new abnormalities noted on ocular examination, including two with cataracts and one with retinal hemorrhages.

Reviewer Comment: The patients with hemochromatosis might be expected to have a relatively more benign natural history than that of the NTDT patients. As such, any positive safety signal would be of interest, but no new safety issues were identified. It is not clear, however, whether a lack of safety events in the hemochromatosis patients was due to true safety of the study drug or to a lack of interaction with the disease in the intended population as might occur for renal toxicity with the NTDT patients. Moreover, treatment on A2202 was for only 1 year, so toxicities from chronic administration would not be evident. As such, the safety data from Study A2202 has limited value.

7.7.3 Safety Findings from Study A2209 Extension Protocol Final Report

Additional analyses of the Extension protocol data were received by the FDA on 11/29/2012, the final study report for the Extension protocol was received on 11/30/2012, and the datasets were received 12/5/2012. The following analyses represent new information to be considered an addendum to the review above. A major revision reported for the final safety analysis was use of MedDRA version 15.0 rather than 14.1 to code the adverse events. For the sake of completeness, critical analyses were repeated using data coded by MedDRA version 15.0 for the Core protocol, and these are provided below with those for the Extension protocol.

7.7.3.1 Exposure

Table 48 shows the duration on active drug by cumulative days of actual dose for the 130 subjects treated in the Extension protocol.

Table 48: Study Drug Exposure in the Study A2209 Extension Protocol

	Grouped by Actual Dose[2]		
Months	**5 mg/kg[2]**	**10 mg/kg[2]**	**20 mg/kg[2]**
0-3	17 (100%)	62 (100%)	38 (100%)
4-6	5 (29%)	54 (87%)	36 (95%)
7-9	5 (29%)	34 (54%)	21 (55%)
>10	4 (24%)	30 (48%)	18 (47%)

[1]Number (%)
[2]Group by actual dose indicated as 5 mg/kg/day (median 5, range 1.8-7.0), 10 mg/kg/day (median 10, actual 7.8-13.3), 20 mg/kg/day (median 20, range 15.0-38.3)

7.7.3.2 Major Safety Results

The numbers of major safety events in the Study A2209 Extension and Core protocols are summarized in Table 49. There are no new events. All events are described in Section 7.3.

Table 49: Summary of Subjects with Major Safety Events in Study A2209

		Core Protocol	
	Extension Protocol (n=130)	Treated (n=110)	Placebo (n=56)
Deaths	0	0	0
Serious Adverse Events	20 (15%)	18 (16%)	8 (14%)
Related Serious Adverse Events	1 (1%)	5 (5%)	0
Drug-Related Discontinuations	4 (3%)	7 (6%)	2 (4%)

7.7.3.3 Supportive Safety Results

Table 50 lists the number of subjects with an adverse event by system organ class in decreasing frequency in the Extension protocol.

Table 50: Adverse Events by SOC For Study A2209

			Core Protocol			
System Organ Class	Extension Protocol (n=130)		Treated (n=110)		Placebo (n=56)	
	n	%	n	%	n	%
Infections and infestations	64	49	51	46	27	48
Gastrointestinal disorders	45	35	35	32	24	43
General disorders and administration site conditions	33	25	27	25	13	23
Nervous system disorders	21	16	17	15	10	18
Musculoskeletal and connective tissue disorders	20	15	14	13	12	21
Respiratory, thoracic and mediastinal disorders	18	14	19	17	9	16
Skin and subcutaneous tissue disorders	17	13	15	14	5	9
Investigations	12	9	13	12	7	13
Blood and lymphatic system disorders	11	8	11	10	2	4
Cardiac disorders	7	5	5	5	4	7
Injury, poisoning and procedural complications	7	5	10	9	5	9
Reproductive system and breast disorders	7	5	8	7	0	0
Eye disorders	6	5	9	8	2	4
Hepatobiliary disorders	6	5	6	5	1	2
Metabolism and nutrition disorders	6	5	4	4	4	7
Ear and labyrinth disorders	5	4	5	5	2	4
Renal and urinary disorders	5	4	6	5	1	2
Psychiatric disorders	3	2	7	6	4	7
Congenital, familial and genetic disorders	2	2	0	0	0	0

Table 50: Adverse Events by SOC For Study A2209

System Organ Class	Extension Protocol (n=130)		Core Protocol			
			Treated (n=110)		Placebo (n=56)	
	n	%	n	%	n	%
Endocrine disorders	2	2	0	0	1	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	2	0	0	0	0
Vascular disorders	2	2	2	2	3	5
Social circumstances	1	1	0	0	0	0
Immune system disorders	0	0	3	3	0	0
Pregnancy, puerperium and perinatal conditions	0	0	3	3	0	0
Surgical and medical procedures	0	0	0	0	1	2

Table 51 lists the number of subjects with adverse events by preferred term in decreasing frequency in the Extension protocol. Only adverse events with a frequency of at least 5% in a treated group are included in the table.

Table 51: Common Adverse Events For Study A2209

Preferred Term	Extension Protocol (n=130)		Core Protocol			
			Treated (n=110)		Placebo (n=56)	
	n	%	n	%	n	%
Any Event	**98**	**75**	**85**	77	**45**	**80**
Upper respiratory tract infection	23	18	15	14	11	20
Diarrhoea	20	15	8	7	6	11
Pyrexia	16	12	12	11	8	14
Abdominal pain upper	15	12	6	5	0	0
Headache	15	12	11	10	8	14
Gastroenteritis	13	10	5	5	2	4
Abdominal pain	12	9	6	5	4	7
Influenza	12	9	6	5	1	2
Nausea	12	9	9	8	7	13
Vomiting	11	8	1	1	4	7
Anemia	8	6	9	8	2	4
Cough	8	6	4	4	4	7
Fatigue	8	6	6	5	4	7
Tonsillitis	8	6	4	4	2	4
Rash	6	5	8	7	3	5
Nasopharyngitis	5	4	9	8	5	9
Rhinitis	5	4	6	5	1	2
Oropharyngeal pain	2	2	10	9	2	4

Table 52 lists the number of subjects with severe adverse events by preferred term in decreasing frequency in the Extension protocol. Only adverse events with a frequency of at least 2% in a treated group are included in the table.

Table 52: Severe Adverse Events For Study A2209

Preferred Term	Extension Protocol (n=130)		Core Protocol			
			Treated (n=110)		Placebo (n=56)	
	n	%	n	%	n	%
Any Event	**19**	**15**	**17**	**15**	**9**	**16**
Abdominal pain	4	3	3	3	0	0
Anemia	4	3	3	3	1	2
Gastroenteritis	5	4	2	2	0	0
Pyrexia	0	0	3	3	0	0

Table 53 lists the number of subjects with adverse events suspected to be related to deferasirox by preferred term in decreasing frequency in the Extension protocol. Only adverse events with a frequency of at least 2% in a treated group are included in the table.

Table 53: Drug-Related Adverse Events For Study A2209

Preferred Term	Extension Protocol (n=130)		Core Protocol			
			Treated (n=110)		Placebo (n=56)	
	n	%	n	%	n	%
Any Event	**27**	**21**	**32**	**29**	**9**	**16**
Diarrhea	7	5	5	5	1	2
Blood creatinine increased	5	4	2	2	0	0
Abdominal pain upper	4	3	3	3	0	0
Headache	4	3	3	3	2	4
Abdominal pain	3	2	2	2	1	2
Nausea	2	2	7	6	4	7
Rash	2	2	7	6	1	2

Table 54 lists the number of subjects with adverse events of special interest as defined in Section 7.1.2. There were no cases of renal tubular dysfunction or peripheral blood cytopenias reported.

Table 54: Adverse Events of Special Interest For Study A2209

Preferred Term	Extension Protocol (n=130)		Core Protocol			
			Treated (n=110)		Placebo (n=56)	
	n	%	n	%	n	%
Increased serum creatinine	5	4	2	2	0	0
Increased liver transaminases	4	3	2	2	0	0
Hearing loss	3	2	1	1	1	2
Lens opacities, retinal changes, optic neuritis	2	2	2	2	1	2
Gastrointestinal hemorrhage, ulcers, esophagitis	3	2	1	1	0	0
Acute renal failure	3	2	2	2	0	0
Hepatic failure	0	0	2	2	0	0

Table 55 lists the number of subjects with critical laboratory test results as defined in Section 7.4.2.1.

Table 55: Critical Laboratory Test Results For Study A2209

Preferred Term	Extension Protocol (n=130)		Core Protocol			
			Treated (n=110)		Placebo (n=56)	
	n	%	n	%	n	%
Platelets <100,000/uL	9	7	6	5	7	13
Neutrophils < 1500/uL	10	8	5	5	4	7
ALT >5x ULN	2	2	1	1	0	0
AST >5x ULN	2	2	1	1	1	2
Creatinine >133% Baseline	3	2	3	3	0	0
Creatinine Clearance <60 mL/min	3	2	3	3	1	2
Urine Protein/Creatinine >1 mg/mg	6	5	5	5	0	0

7.7.3.4 Other Safety Explorations

The median duration of exposure across protocols was 23 months (range, <1-27 months), and 72% of subjects completed at least 18 months on study. There were 24 subjects who reached an LIC <3 mg Fe/g dw and interrupted treatment. The sponsor provided an analysis of adverse events grouped by the minimum LIC achieved through the Core and Extension protocols (Additional Analyses Table 2-1). The results were similar to those discussed in Section 7.5.4 for the first 20 subjects. The sponsor concluded that the results were comparable across the groups reaching different minimum LICs. This reviewer also evaluated the suspected adverse reaction by the minimum LIC reached (Table 56).

Table 56: Suspected Adverse Events by Minimum LIC

Preferred Term	Minimum LIC (mg Fe/g dw)			
	>3 (n=134)		<3 (n=24)	
	n	%	n	%
Nausea	5	4	3	13
Abdominal pain upper	4	3	2	8
Rash	7	5	2	8
Abdominal pain	4	3	1	4
Blood creatinine increased	5	4	1	4
Decreased appetite	0	0	1	4
Diarrhoea	10	7	1	4
Lethargy	0	0	1	4
Pain	0	0	1	4
Rash papular	0	0	1	4
Rash pruritic	0	0	1	4
Somnolence	0	0	1	4
Vomiting	2	1	1	4
Headache	4	3	0	0

Reviewer Comment: The final results of the Extension protocol confirm the previous findings that the safety profile in the NTDT population was comparable to that in the patients with iron overload due to transfusions. There remains concern about the potential for additional safety issues with long-term use that cannot be determine from this study with short follow-up.

8 Postmarket Experience

The Periodic Safety Update Report (PSUR) for the period 11/01/2010 to 10/31/2011 (dated 12/20/2011) was reviewed. The following information was provided in this PSUR:

Worldwide marketing authorization status

Exjade is marketed in 113 countries. During the reporting period, there were no marketing authorization withdrawals or suspensions, no refusals to grant a marketing authorization renewal, no restrictions on distribution, and no clinical trial suspensions for safety reasons occurred.

Estimated exposure

During the reporting period, approximately 1514 patients received treatment with deferasirox in Novartis-sponsored clinical trials. On the basis of sales volume, the applicant estimated that approximately (b) (4) patients were exposed to marketed drug during the reporting period. A summary of the estimates of use of marketed drug by diagnosis as provided by the applicant is shown in Table 57.

Table 57: Estimated Annual Exposure to Marketed Drug

Diagnosis	Number of patients (%) in the EU	Number of patients (%) in the US
Thalassemia		(b) (4)
Sickle cell disease		
Myelodysplastic syndrome		
Other anemias		

Actions taken in the reporting period for safety reasons

During the reporting period the applicant issued a Dear Doctor Letter in Saudi-Arabia to provide physicians with additional guidance on patient monitoring in order to ensure appropriate use of Exjade.

Changes to reference safety information

During the reporting period, the safety core data sheet was updated to indicate that for patients with moderate hepatic impairment the starting dose should be reduced by approximately 50%, and that Exjade should not be used in patients with severe hepatic impairment. In addition, tubulointerstitial nephritis was added as an adverse drug reaction.

Safety findings from marketing experience

A total number of 5485 cases involving 13,088 adverse reactions were received during the reporting period. Table 58 summarizes these events by SOC. These cases included numerous

reports of deaths, most due to the primary disorder. In 160 cases, however, progression of underlying diseases was not cited as the cause. These deaths are also summarized in Table 58.

Table 58: Marketed Drug Adverse Reactions and Deaths by SOC in the Reporting Period

	Adverse Reactions (n=13,088)		Deaths[1] (n=160)	
	Number	%	Number	%
Gastrointestinal disorders	3114	24	10	6
General disorders and administration site conditions	1956	15	8	5
Investigations	1715	13	1	<1
Skin and subcutaneous tissue disorders	729	6		
Infections and infestations	710	5	51	32
Nervous system disorders	615	5	17	10
Renal and urinary disorders	462	4	4	3
Respiratory, thoracic and mediastinal disorders	457	3	13	8
Congenital, familial and genetic disorders	412	3	1	<1
Injury, poisoning and procedural complications	378	3	11	7
Musculoskeletal and connective tissue disorders	368	3		
Neoplasms benign, malignant and unspecified	344	3	2	1
Metabolism and nutrition disorders	319	2		
Blood and lymphatic system disorders	293	2	1	<1
Eye disorders	252	2		
Hepatobiliary disorders	210	2	9	6
Cardiac disorders	196	1	30	19
Psychiatric disorders	149	1		
Vascular disorders	136	1	1	<1
Ear and labyrinth disorders	124	1		
Immune system disorders	55	<1		
Surgical and medical procedures	31	<1		
Reproductive system and breast disorders	24	<1		
Social circumstances	20	<1	1	<1
Pregnancy, puerperium and perinatal conditions	14	<1		
Endocrine disorders	5	<1		

[1]Deaths not due to underlying disease.

There were five cases of overdose reported. Narratives provided by the applicant are:

- A 55-year-old male patient received Exjade at a dose of 1500 mg Q8H (total daily dose 4500 mg) from (b) (6) for sickle cell anemia. On an unspecified date the patient died (cause of death not stated).
- A 58-year-old male patient was receiving Exjade 2500 mg QD for an iron metabolism disorder. On an unspecified date his physician increased the dose of Exjade (not specified) and he was subsequently admitted to hospital for "drug overload."
- A 7-year-old female child accidentally received 3 x 500 mg tablets, instead of 1 x 500 mg. The patient's previous prescription had been 3 x 125 mg tablets. There was no adverse event reported.
- A 9-year-old male child received Exjade at 30 mg/kg for iron overload secondary to thalassemia major from (b) (6). In (b) (6) he experienced appendicitis, and on (b) (6)

(b) (6) he experienced a post-pyloric stomach perforation. The reporting physician considered the overdose of Exjade to be an alternative cause for the events.

- A female patient received Exjade at a dose of 5000 µg/kg for cardiac siderosis from (b) (6) the patient experienced paresthesia and myoclonus of the lower limbs. Exjade was discontinued the same day and the events recovered on 17 Jun 2011.

Cumulatively there have been 162 cases of exposure in pregnancy. There were five cases with fetal or neonatal abnormalities reported. Of the two with live births, one neonate had jaundice that resolved completely, and the other was at risk of renal impairment due to drepanocytosis. Of the three elective terminations, one involved conjoined twins, and the other two had unspecified abnormalities.

Significant findings from clinical trials during the reporting period
(Tabulation provided by the applicant)

Table 59: Summary of Safety Findings from Clinical Trials

Study number	Title (abbreviated)	Subjects	Safety findings
CICL670AUS03E	Extension trial in patients with MDS/ Open-label extension phase/Long-term safety and tolerability	83	The rates of suspected moderate/severe AEs, and AEs that led to study drug discontinuation during the 3-year period of the study were similar in the normal and abnormal baseline serum creatinine group (78.5% versus 79.2% suspected moderate/severe AEs; 24.2% versus 29.2% AEs that led to study drug discontinuation). The one exception was blood creatinine increased which was reported more frequently in the abnormal baseline serum creatinine group (29.2%) than in the normal baseline serum creatinine group (5.7%). The rate of death was higher in the normal (16.8%) than in the abnormal baseline serum creatinine group (12.5%), although the number of patients in the abnormal baseline serum creatinine group is small. None of the deaths were suspected to be related to deferasirox.
CICL670AUS04	Open label trial evaluating cardiac T2* in b-thalassemia patients on deferasirox treatment for 18 Months	28	Two patient deaths occurred following withdrawal from the trial due to SAEs. One patient died due to congestive heart failure and the other patient's death was secondary to multi-organ failure. These deaths, including the antecedent AEs, were not assessed as related to study drug.
CICL670A2125	PK study in patients with impaired hepatic function and healthy subjects with normal hepatic function/	20	Adverse events suspected to be study drug related by PT were headache, erythropenia, hyperuricemia and genital herpes. None of the subjects died or experienced an SAE or an AE that led to discontinuation from the study.
CICL670A2209	A randomized, double-blind, placebo controlled, phase II study to evaluate efficacy and safety of deferasirox in non-	166	No new safety signals were identified. Overall, the most frequent AEs (at least 10% in any either deferasirox group or the combined placebo group) were headache, upper respiratory tract infection, oropharyngeal pain, pyrexia, rash and nausea. SAEs were reported for 24 patients and were comparable

Table 59: Summary of Safety Findings from Clinical Trials

Study number	Title (abbreviated)	Subjects	Safety findings
	transfusion dependent thalassemia patients with iron overload		between the deferasirox and placebo treatment groups. SAEs were slightly more frequent in the 10 mg/kg/day dose groups than in the 5 mg/kg/day dose groups. No deaths occurred during the study.
CICL670A2201	Open study in patients with SCD comparing ICL670 to deferoxamine (DFO) subcutaneous/ Randomized open-label, phase II/Safety based on AEs and laboratory parameters	212	AEs observed in this study are consistent with the known safety profile of ICL670; no specific safety concerns were evident. Two deaths were reported in this study, with 1 of the deaths in the ICL670 treatment arm; neither death was attributed to study drug.
CICL670A2409E	Three-year cardiac sub-study to Study CICL670A2409: in patients diagnosed with transfusion-dependent iron overload	86	The incidence of grouped AEs reported in the study (rash, abdominal pain, nausea,vomiting, diarrhea, gastroenteritis) is as expected from the safety profile of deferasirox. SAEs were suspected to be related to study medication, and none of these led to discontinuation of study medication. Majority of the SAEs were from the Infections and Infestations SOC. No deaths were observed during the study.

Risk Management Activities

Important risks for monitoring as identified by the applicant:

• Identified risk: Increased serum creatinine, acute renal failure, renal tubular disorders (including acquired Fanconi's syndrome), increased liver transaminases, gastrointestinal hemorrhage and ulcers; esophagitis, hearing loss, lens opacities, retinal changes and optic neuritis.

• Potential risks: Hepatic failure (the search includes hepatic encephalopathy) and peripheral blood cytopenias. Infections (with Mucormycosis, Yersinia, Klebsiella, Pseudomonas, E. coli), severe skin reactions (including leukocytoclastic vasculitis and DRESS), alopecia (in children), hypocalcaemia, cardiac arrhythmia, central nervous system disorders, (hepatic encephalopathy and ischemic and hemorrhagic cerebrovascular disorders), stomatitis and mouth ulceration were previously identified as additional relevant safety findings for close monitoring.

In the latest version of the Risk management plan (dated 11/8/2011), long-term exposure in NTDT patients was added as an on-going safety concern. The proposed pharmacovigilance activities to address this included routine pharmacovigilance activities and the one-year extension phase of Study A2209. The proposed risk minimization activities for this issue included risk and risk management communication in the prescribing information.

On-going safety studies are summarized in Table 60 (provided by the applicant). Preliminary information was included for two of these studies:

- In the RMP Study - There was one event reported as an adverse drug reaction to deferasirox, and this related to an abnormal renal function test. This event occurred in a 75 year old female patient. Follow up information is not yet available.

- In ICL670A1401 - An analysis was done as of 8/31/2011 when 3169 subjects were enrolled. Safety data was available for 2301 patients treated for at least 6 months. Common adverse reactions included blood creatinine increased (9.5%), renal impairment (8.7%), diarrhea (6.6%), nausea (4.9%), renal disorder (4.9%), rash (4.3%), decreased appetite (3.2%), BUN increased (3.1%), hepatic function abnormal (2.8%), alkaline phosphatase increased (2.0%), liver disorder (2.0%), AST increased (1.8%), rash generalized (1.7%), ALT increased (1.7%), gamma-GTP increased (1.4%), abdominal discomfort (1.4%), vomiting (1.4%), and pyrexia (1.2%).

Table 60: On-Going Safety Studies

Study number	Study Title	Subjects
CICL670A2123	Study of renal hemodynamics in βthalassaemia patients treated with Exjade /Openlabel phase I/ Change in renal blood flow/GFR	16
CICL670A2411	Registry study of children aged 2 to < 6 years with transfusional hemosiderosis treated with Exjade/Observational/Renal and hepatic safety	200
CICL670A2204	Open safety trial in patients with chronic anemia and transfusional iron overload/Open non-comparative phase II/ Efficacy based on (liver iron content (LIC).	114
CICL670A2204E	Extension trial in patients with chronic anemia and transfusional hemosiderosis/One year, open-label extension phase/Long-term safety and tolerability	130
CICL670A2206	Cardiac iron overload due to chronic transfusions/ multicenter, randomized, open-label, non-inferiority study comparing Exjade to DFO/Relative change in myocardial T2* after 12 months	192
CICL670A2209E1	A one-year open-label extension to a randomized, double-blind, placebo-controlled, phase II study to evaluate efficacy and safety of deferasirox in non-transfusion-dependent thalassemia patients with iron overload	133
CICL670A2301	Sentinel site Monitoring Study	300
CICL670AFR01T	International sentinel site surveillance (prospective observational study) of patients treated with Exjade	300
CICL670AUS32	Exjade food interaction study: A single-arm, open-label study of the palability and tolerability of Exjade with meals with different liquids or crushed or added to food	60
CICL670F2101	A randomized, open-label, single-center, four-period, cross-over study evaluating the bioavailability of deferasirox (single dose) from three formulations	20
RMP study	Prescription Event Monitoring (PEM) study	300
ICL670A1401	Japanese Drug Use Investigation	3500
ICL670A1402	Japanese Special Investigation	900

Lack of efficacy

There were 213 cases reporting lack of efficacy. These included 70 reports of disease progression with no other events related to drug ineffective, 96 reports of drug ineffective and additional drug ineffective related event, 46 reports of ferritin increase with no other drug ineffective related events, and 1report of disease progression and ferritin increase. The applicant noted that the doses of deferasirox described in these reports seem to be at the lower range of the recommended dose. As such these cases do not necessarily correspond to lack of efficacy.

Overall safety assessment by the applicant:

- The majority of events come from the EPASS program, and these have poor documentation, making assessment of the events difficult.
- The review of mortality indicated that most deaths were due to underlying disease.
- Long-term exposure in NTDT patients was added as missing information to the Risk Management Plan.
- The review of rhabdomyolysis reports yielded a single suspected event. Reviews for rhabdomyolysis will continue in the next PSUR.
- The reviews of hemorrhagic events, anemia, hemolytic anemia and stomatitis were confounded by the underlying disease.
- A review of renal events revealed no new safety concern. A relationship with Exjade is still suspected. The report indicated that a high proportion of cases of renal tubulopathies occurred in young patients with thalassemia, and these changes are usually reversible.
- The applicant concluded that the safety data remain consistent with the previous cumulative experience as presented in the safety core data sheet as revised in the reporting period.

9 Appendices

9.1 Advisory Committee Meeting

An Advisory Committee did not discuss this application.

9.2 Literature Reviewed/ References

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/s/

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