



Australian Government  
Department of Health  
Therapeutic Goods Administration

## AusPAR Attachment 2

# Extract from the Clinical Evaluation Report for deferasirox

Proprietary Product Name: Exjade

Sponsor: Novartis Pharmaceuticals Australia Pty  
Ltd

**Date of CER: March 2013**

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## About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
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## List of abbreviations

Abbreviation	Meaning
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AUCinf	Area under the time curve from time zero to infinity
AUClast	Area under the time curve from time zero to the last measurable concentration sampling time
CI	Confidence interval
Cmax	Maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration
CSR	Clinical Study Report
dw	dry weight
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HH	Hereditary Haemochromatosis
HR	Heart rate
ICL670	Deferasirox
IVRS	interactive voice response system

Abbreviation	Meaning
L	Litre
LIC	liver iron concentration
LLN	Lower limit of normal
NTDT	Non-transfusion-dependent thalassaemia
PK	pharmacokinetic
PP	Per protocol
PPS	Per protocol set
qd	Once daily
SD	Standard Deviation
SOC	System Organ Class
SRN	safety-related notifications
t <sub>1/2</sub>	Half-life associated with the terminal slope
T <sub>max</sub>	Time to reach C <sub>max</sub>
ULN	Upper limit of normal
UPCR	urinary protein/creatinine ratio

## 1. Introduction

Deferasirox is an orally active N-substituted bis-hydroxyphenyl-triazole tridentate iron chelating agent. The sponsor had stated that deferasirox is highly selective for iron and that it binds iron with high affinity in a 2:1 ratio. Deferasirox promotes excretion of iron, primarily in the faeces.

The currently approved indications as stated in the Australian PI for deferasirox are:

*The treatment of chronic iron overload due to blood transfusions (transfusional haemosiderosis) in adults and paediatric patients 6 years and older. Exjade is also indicated for the treatment of chronic iron overload in paediatric patients aged 2 to 5 years who are unable to take desferrioxamine therapy or in whom desferrioxamine has proven ineffective.*

This submission is an application to extend the indications of deferasirox to include the treatment of chronic iron overload in patients (aged 10 years and older) with non transfusion dependent thalassaemia (NTDT), with the following proposed indication:

*Exjade is also indicated for the treatment of chronic iron overload in patients with nontransfusion-dependent thalassemia syndromes aged 10 years and older.*

The dose regimen for the currently approved indication of transfusional iron overload is a recommended initial daily dose of deferasirox of 20 mg/kg body weight.<sup>1</sup> Treatment with Exjade is recommended to be started after transfusion of approximately 20 units (about 100 mL/kg) of packed red blood cells or when there is evidence from clinical monitoring that chronic iron overload is present (for example serum ferritin greater than 1000 µg/L). Subsequently, it is recommended that serum ferritin be monitored every month and that the dose of deferasirox be adjusted (in steps of 5 to 10 mg/kg) if necessary every 3 to 6 months based on the trends in serum ferritin. Doses above 40 mg/kg are not recommended due to limited experience with doses above this level. For patients whose serum ferritin level has reached the target level (usually between 500 and 1000 µg/L), dose reductions in steps of 5 to 10 mg/kg should be considered to maintain serum ferritin levels within the target range. If serum ferritin consistently falls below 500 µg/L, an interruption of treatment should be considered.

The proposed dose regimen for the additional indication of iron overload in patients with NTDT is a recommended initial daily dose of deferasirox of 10 mg/kg body weight. Treatment should only be initiated when there is evidence of iron overload (liver iron concentration (LIC) greater than or equal to 5 mg Fe/g dry weight (dw) or serum ferritin consistently greater than 800 µg/L). Subsequently, it is recommended that serum ferritin be monitored every month and that a dose increase in increments of 5 to 10 mg/kg be considered every 3 to 6 months of treatment if the patient's LIC is greater than or equal to 7 mg Fe/g dw, or serum ferritin is consistently greater than 2000 µg /L and not showing a downward trend, and the patient is tolerating the drug well. Doses above 20 mg/kg are not recommended as there is no experience with doses above this level in patients with NTDT. In patients in whom LIC was not assessed and serum ferritin is less than or equal to 2000 µg /L, dosing should not exceed 10 mg/kg. For patients in whom the dose was increased to greater than 10 mg/kg, dose reduction is recommended to 10 mg/kg or less when LIC is less than 7 mg Fe/g dw or serum ferritin is less than or equal to

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<sup>1</sup> An initial daily dose of 30 mg/kg may be considered for patients receiving more than 14 mL/kg/month of packed red blood cells (approximately > 4 units/month for an adult), and for whom the treatment objective is reduction of iron overload. An initial daily dose of 10 mg/kg may be considered for patients receiving less than 7 mL/kg/month of packed red blood cells (approximately < 2 units/month for an adult), and for whom the treatment objective is maintenance of the body iron level.

2000 µg /L. Once a satisfactory body iron level has been achieved (LIC less than 3 mg Fe/g dw or serum ferritin less than 300 µg/L), treatment should be interrupted, and re-initiated when there is evidence from clinical monitoring that chronic iron overload is present.

Doses (in mg/kg) are to be calculated and rounded to the nearest whole tablet size. The tablets are to be dispersed by stirring in water, orange or apple juice until a fine suspension is obtained. After the suspension has been swallowed, any residue should be resuspended in a small volume of water or juice and swallowed. Deferasirox dispersible tablets should not be dispersed in milk or carbonated drinks (due to issues of foaming and slow dispersion, respectively) and should not be chewed or swallowed whole.

## 2. Clinical rationale

Chronic iron overload may result from repeated transfusions (transfusional hemosiderosis) or from an increased intestinal absorption of iron, which is the primary source of iron overload in conditions such as hereditary hemochromatosis (HH) and NTDT. Untreated chronic iron overload can result in complications such as liver abnormalities as well as cardiac, metabolic and endocrine disturbances.

Patients with NTDT (for example beta thalassaemia intermedia, HbE beta thalassaemia, and HbH alpha thalassaemia) are part of the clinical spectrum of thalassaemia syndromes. They have milder anaemia compared to thalassaemia major and therefore require no or only occasional blood transfusions. Nevertheless, NTDT patients do, over time, develop clinically relevant iron overload, mainly due to an increased intestinal absorption of iron, driven by anaemia secondary to ineffective erythropoiesis.

Iron chelation treatment regimen for NTDT patients is different from that established for transfusional iron overload due to their lower rate of ongoing iron accumulation. Contrary to patients who are regularly transfused and where iron chelation is lifelong, NTDT patients require only intermittent chelation therapy with lower doses to reduce iron burden to levels below that associated with morbidities. This would be followed by a few years of a drug “holiday” due to the slower accumulation of iron compared to transfusional iron overload, until the patient has accumulated clinically relevant iron overload again.

The sponsor had stated that the iron chelators deferoxamine (desferal; desferrioxamine) and deferiprone (ferriprox) have been used to reduce iron in patients with NTDT, but neither agent has been prospectively investigated in controlled clinical trials. In addition, phlebotomy, the standard therapy to remove excess iron in patients with HH, is contraindicated in patients with NTDT due to the underlying anaemia. The sponsor is therefore of the opinion that deferasirox can be a suitable treatment option in NTDT patients with iron overload, especially in view of its convenient dosing regimen of per oral administration once daily.

Comments: The clinical rationale is sound and logical. The pathophysiology of iron overload in patients with NTDT is postulated to be due to ineffective erythropoiesis resulting in chronic anaemia and hypoxia, which lead to suppression of hepcidin as a compensatory response. This in turn leads to an increase in intestinal absorption of iron as well as an increase in the release of recycled iron from the reticuloendothelial system. In Australia, neither desferal nor ferriprox is approved for the indication of iron overload in patients with NTDT. The approved indication for desferal is

*the treatment of acute iron intoxication and of chronic iron overload due to transfusion-dependent anaemias*

and that for ferriprox is

*the treatment of iron overload in patients with thalassaemia major who are unable to take desferrioxamine or in whom desferrioxamine therapy has proven ineffective.*

## 2.1. Orphan drug designation

Deferasirox was designated as an orphan drug by the TGA in 2004, for the currently approved indication of

*treatment of chronic iron overload in patients with transfusion-dependent anaemias.*

This submission does not contain any information regarding orphan drug designation of deferasirox for the proposed additional indication.

## 3. Contents of the clinical dossier

### 3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- 3 clinical pharmacology studies
- These consist of 1 pharmacokinetic study (A2125) evaluating the use of deferasirox in subjects with hepatic impairment, and 2 drug-drug interactions (DDI) studies (A2126 and A2129). Study A2126 was a DDI study of deferasirox with midazolam, and Study A2129 was a DDI study of deferasirox with cholestyramine.
- 1 pivotal efficacy/safety study (Study A2209)
- 1 other efficacy/safety study (Study A2202).

In this evaluation, Study A2209, a randomised double blind, placebo controlled Phase II study in NTDT patients with iron overload, will be evaluated as the pivotal efficacy/safety study, while Study A2202, an open label, dose escalation Phase I/II study in patients with iron overload resulting from hereditary haemochromatosis, will be evaluated as a supporting efficacy/safety study.

### 3.2. Paediatric data

The submission included paediatric efficacy/safety data. Study A2209 was conducted in a patient population aged greater than or equal to 10 years.

### 3.3. Good clinical practice

The clinical studies reviewed in this evaluation were in compliance with CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice.<sup>2</sup>

## 4. Pharmacokinetics

### 4.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

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<sup>2</sup> The Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) <<http://www.tga.gov.au/industry/clinical-trials-note-ich13595.htm>>



**Table 1. Submitted pharmacokinetic studies.**

PK topic	Subtopic	Study ID	*
	Hepatic impairment	A2125	To evaluate the PK of a single dose of 20 mg/kg deferasirox in subjects with impaired hepatic function and in healthy subjects.
PK interactions	deferasirox with midazolam	A2126	To investigate the effect of deferasirox on the PK of midazolam in healthy volunteers.
	deferasirox with cholestyramine	A2129	To assess the effect of cholestyramine on single dose PK of deferasirox in healthy volunteers.

\* Indicates the primary aim of the study.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

## 4.2. Summary of pharmacokinetics

### 4.2.1. Pharmacokinetics in other special populations

#### 4.2.1.1. Pharmacokinetics in subjects with impaired hepatic function

Results in Study A2125 showed that, compared to the healthy control group, deferasirox AUC<sub>inf</sub> was increased by 16% in the mild hepatic impairment group and by 76% in the moderate hepatic impairment group, while C<sub>max</sub> was increased by 22% in both the mild and the moderate hepatic impairment groups. The mean half life of deferasirox was comparable across the healthy control, mild hepatic impairment and moderate hepatic impairment groups.

### 4.2.2. Pharmacokinetic interactions

#### 4.2.2.1. Pharmacokinetic interactions demonstrated in human studies

Results in Study A2126 showed that there was a reduction of 17% in midazolam exposure and reduction of 23% in midazolam C<sub>max</sub>, when midazolam was administered with deferasirox, compared to when midazolam was administered alone.

Results in Study A2129 showed that co administration of cholestyramine reduced deferasirox exposure by 45% and C<sub>max</sub> by 12%, compared to when deferasirox was administered alone. This decrease in systemic exposure could be attributed to the cholestyramine binding of the conjugated deferasirox that was excreted into the gastrointestinal via biliary excretion, thereby reducing subsequent reabsorption and hence systemic exposure.

## 4.3. Evaluator's overall conclusions on pharmacokinetics

The proposed changes to the currently approved PI for deferasirox relating to dose adjustment for patients with moderate hepatic impairment, based on the results of Study A2125, are appropriate. The main findings of studies A2126 and A2129 are reasonably reflected in the relevant safety related notifications in the existing PI.

## 5. Pharmacodynamics

Not applicable.

## 6. Dosage selection for the pivotal studies

The rationale provided by the sponsor for the dose of deferasirox used in the pivotal study (Study A2209) is described and discussed below

## 7. Clinical efficacy

For the proposed indication of treatment of chronic iron overload in patients with NTDT syndromes aged 10 years and older.

### 7.1. Pivotal efficacy studies

#### 7.1.1. Study A2209

##### 7.1.1.1. Study design, objectives, locations and dates

Study A2209 was a randomised, double blind, placebo controlled, multi centre Phase II study evaluating the efficacy and safety of deferasirox in NTDT patients with iron overload. Two starting doses of deferasirox (5 and 10 mg/kg/day) were evaluated. Subjects were randomised in a 2 to 1:2 to 1 ratio to 1 of 4 treatment groups: 5 mg/kg/day deferasirox, placebo matching 5 mg/kg/day deferasirox, 10 mg/kg/day deferasirox, and placebo matching 10 mg/kg/day deferasirox. Subjects received treatment for 52 weeks. Doubling of the randomisation dose (up to 20 mg/kg/day) was considered after 24 weeks of treatment in subjects with less than 15% decrease from baseline in liver iron content (LIC) and with LIC greater than or equal to 7 mg Fe/g dry weight (dw). At the end of study, subjects could enter a one year open label extension study. The clinical study report (CSR) submitted for this application presents only the results for the 52 week double blind phase.

The primary objective of the study was to compare the efficacy of the 2 dose regimens of deferasirox (starting doses of 5 and 10 mg/kg/day) with that of placebo in patients with NTDT, based on change in LIC from baseline after one year of treatment. The secondary objectives of the study included comparing the efficacy of the 2 dose regimens of deferasirox with that of placebo, based on change in LIC from baseline after 6 months of treatment, comparing the change in serum ferritin over one year of treatment between deferasirox and placebo, evaluating the relationship between serum ferritin and LIC, evaluating the efficacy and safety of dose doubling of deferasirox, and evaluating the safety of the 2 dose regimens of deferasirox versus placebo in NTDT patients.

This was a multi centre study where subjects were enrolled in a total of 27 study sites across 9 countries: 2 in Greece, 6 in Italy, 1 in the Lebanon, 4 in Malaysia, 1 in Taiwan, 4 in Thailand, 4 in Turkey, 2 in the United Kingdom, and 3 in the US. According to the sponsor, sites from Mediterranean and Asian countries had been deliberately included in the study as NTDT is most prevalent in populations of these geographical areas. The study start date (first subject enrolled) and end date (last patient completed) were 24 November 2008 and 22 June 2011, respectively.

##### 7.1.1.2. Inclusion and exclusion criteria

Subjects enrolled in this study were male or female subjects greater than or equal to 10 years of age (greater than or equal to 18 years in Greece only, due to a local country amendment) with NTDT syndromes, who had not received any transfusion within 6 months prior to entry into the

study, with LIC greater than or equal to 5 mg Fe/g dw (measured by R2-MRI) and with serum ferritin greater than 300 µg/L at screening (two consecutive values at least 14 days apart). Subjects with anticipated regular transfusion program during the study, or who had chelation within 1 month prior to study start were excluded.

Comments: The inclusion and exclusion criteria were appropriate and aimed to recruit patients with NTDT with evidence of iron overload. There is limited data and no internationally accepted guidelines on the management of iron overload in patients with NTDT, especially with regards to clinical guidelines on when iron chelation therapy should be started. A literature search<sup>3</sup> showed mention of criteria for initiation of iron chelation therapy in NTDT patients as LIC greater than 3 to 6 mg Fe/g dw and/or serum ferritin level greater than or equal to 500 µg/L.

### 7.1.1.3. Study treatments

The randomised starting dose of deferasirox or placebo was either 5 mg/kg/day or 10 mg/kg/day.

LIC was measured after 24 weeks of treatment, and if this Week 24 LIC assessment indicated insufficient iron chelation (that is LIC greater than or equal to 7 mg Fe/g dw and LIC reduction less than 15% compared to baseline<sup>4</sup>), the dose of deferasirox or placebo could be doubled. If a subject had a Week 24 LIC less than 3 mg Fe/g dw, treatment with study drug was to be interrupted until the next LIC assessment was above 5 mg Fe/g dw, even when serum ferritin remained below 300 µg/L. However, these subjects were not to be discontinued from the study and were to continue their monthly visits. The dose of study drug was also adapted to the patient's body weight throughout the course of the study. If the serum ferritin level fell to less than 100 µg/L at any visit, the study drug was to be withheld and the LIC assessed. If LIC was less than 3 mg Fe/g dw, study treatment was to be stopped and the study drug withheld until the LIC was greater than or equal to 5 mg Fe/g dw and serum ferritin was greater than 300 µg/L. The total treatment duration for the double blind phase was 52 weeks.

With regards to the selection of the deferasirox doses to be tested in Study A2209, the sponsor had stated that the study treatment regimens of deferasirox (starting doses of 5 and 10 mg/kg/day) had been chosen based on the estimated mean efficiency of deferasirox for daily iron removal from previous studies in patients with transfusional iron overload (1 mg/kg of deferasirox is expected to eliminate 0.021 mg Fe/kg). It was estimated that 6 months of treatment with 5 mg/kg/day and 10 mg/kg/day deferasirox would reduce LIC by 1.8 and 3.6 mg Fe/g dw, respectively, and for 12 months, these estimates would be doubled. Taking into consideration the LIC threshold of 5 mg Fe/g dw and a constantly increased gastrointestinal iron intake in NTDT patients of up to 1 to 3.5 grams per year (which would translate to an LIC increase of up to 1.5 to 4.9 mg Fe/g dw in a 60 kg patient), the sponsor estimated that the treatment regimens of 5 to 10 mg/kg/day deferasirox would be unlikely to cause over chelation but could have the potential to remove significant amounts of iron resulting in a significant difference when compared to placebo treated patients.

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<sup>3</sup> Galanello and Origa, Beta Thalassaemia. *Orphanet Journal of Rare Diseases*, 5:11, 2010; Ladis *et al*, Deferasirox administration for the treatment of non-transfusional iron overload in patients with thalassaemia intermedia. *British Journal of Haematology*.151:504-8, 2010; Olivieri, Iron Overload and Iron-Chelating Therapy in Thalassaemia Intermedia. *The Genetic Resource*, Vol 11, No. 2, 1997; Olivieri *et al*, Iron-Chelating Therapy and the Treatment of Thalassaemia. *Blood*, Vol 89, No. 3, 1997; Thalassaemia International Federation, Addressing the Management of Non-Transfusion-Dependent Thalassaemias (NTDT). Position paper 5.2, March 2012.

<sup>4</sup> The clinical study report is inconsistent in stating the criterion with regards to the absolute LIC level, stating it as LIC greater than or equal to 7 mg Fe/g dw in some instances or sections and LIC greater than 7 mg Fe/g dw in others. This will be raised as a clinical question. For the purpose of this evaluation report, a criterion of LIC greater than or equal to 7 mg Fe/g dw will be used throughout for consistency.

Comments: The rationale for the study dose selection is sound. The study design involving a placebo control is appropriate.

#### **7.1.1.4. Efficacy variables and outcomes**

The primary efficacy variable was the absolute change from baseline in LIC<sup>5</sup> at Week 52. The primary efficacy outcome was a comparison of the efficacy of the 2 dose regimens of deferasirox (starting doses of 5 and 10 mg/kg/day) with that of placebo in patients with NTDT based on absolute change in LIC from baseline at Week 52.

Other efficacy endpoints included absolute change from baseline in LIC at Week 24, serum ferritin quarterly change from baseline,<sup>6</sup> correlation between serum ferritin and LIC, efficacy of dose doubling, and analyses of exploratory haematological and iron metabolism parameters.<sup>7</sup>

Comments: Overall, the primary and secondary endpoints of this study are appropriate and allowed evaluation of the effect of deferasirox on change from baseline in LIC after 52 weeks of treatment (primary endpoint) and after 24 weeks of treatment, effect of deferasirox on serum ferritin as well as exploration of the efficacy of dose doubling of deferasirox and correlation between serum ferritin and LIC. The efficacy endpoints did not include evaluation of effect on survival, relief of symptoms or end organ damage arising from chronic iron overload. However, although there are no established guidelines regarding appropriate study endpoints for iron chelators, it is noted by the evaluator that the currently approved indication for Exjade in patients with transfusional overload was based on studies with LIC as endpoints (as presented in the currently approved PI for Exjade).

#### **7.1.1.5. Randomisation and blinding methods**

Subjects were randomised in a 2 to 1:2 to 1 ratio to receive 5 mg/kg/day of deferasirox, placebo matching 5 mg/kg/day of deferasirox, 10 mg/kg/day of deferasirox, and placebo matching 10 mg/kg/day of deferasirox. Interactive voice response system (IVRS) was used for randomisation and study drug dispensation. The sponsor had stated that due to the geographical distribution of NTDT patients and the fact that these patients were primarily treated in specialist centres, no stratification by centre was done.

This was a double blind study. Blinding only applied to the treatment (that is deferasirox or placebo), and the dose was not blinded as the blinding of dose was not considered feasible. After signing the informed consent form, the patient was assigned a patient number by the investigator. The investigator then contacted the IVRS which assigned the patient a randomisation number. Each study site was supplied by the sponsor with study drugs in identically appearing packaging. The investigator site identified the study drug package to be dispensed to the patient by calling the IVRS and obtaining the medication number.

#### **7.1.1.6. Analysis populations**

Three analysis sets were defined in the study. The Full Analysis Set (FAS) consisted of all randomised subjects, and these subjects were analysed according to the treatment group to which they were randomised, with the 2 placebo groups pooled for efficacy analyses. The Per Protocol Set (PPS) consisted of all treated subjects from the FAS who had no blood transfusion from 6 months prior to study start to the end of study visit (that is Week 52), had both a

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<sup>5</sup> Liver iron content was estimated throughout the study by the use of a magnetic resonance imaging technique called R2-MRI.

<sup>6</sup> The sponsor had stated that the quarterly average of all serum ferritin measurements was used instead of single readings at Week 24 or Week 52 in order to compensate for the variability of serum ferritin.

<sup>7</sup> Total serum iron, serum transferrin, transferrin saturation, soluble transferrin receptor, non-transferrin-bound iron (NTBI), labile plasma iron (LPI), reticulocyte count, nucleated red blood cell count (NRBC), haemoglobin, plasma haemoglobin, plasma haptoglobin, lactate dehydrogenase (LDH), serum erythropoietin, plasma hepcidin and growth differentiation factor (GDF15)

baseline and at least one post baseline LIC assessment, and had no other major protocol deviation. These subjects were analysed according to the treatment regimen they were randomised to, with the 2 placebo groups pooled for analyses. The Safety Set consisted of all randomised subjects who had received at least one dose of study drug. These subjects were analysed according to the first treatment received and the first daily dose actually administered. The 2 placebo groups were displayed separately as well as pooled together as one placebo group in all safety analyses.

The FAS was the primary analysis set for efficacy analyses. The PPS was used for pre specified sensitivity analyses of the efficacy endpoints. The Safety Set was used for the safety analyses.

Comments: The definitions of the analysis populations are in keeping with the TGA adopted ICH E 9 Statistical Principles for Clinical Trials. The efficacy analyses were performed on the FAS in accordance with the intent to treat principle.

#### **7.1.1.7. Sample size**

The sponsor had estimated the sample size to obtain 90% power for showing superiority of at least one of the deferasirox treatment groups over placebo with respect to change from baseline in LIC at Week 52. Based on the assumptions of one sided family wise type I error probability of  $\alpha=0.025$ , a true mean decrease of 3 mg Fe/g dw in LIC change at Week 52 compared to placebo, and a true standard deviation of 4 mg Fe/g dw for change from baseline in LIC at Week 52, it was calculated that a sample size of 46 subjects in each deferasirox group and 23 in each matching placebo group (that is 138 subjects in total) would be sufficient to achieve 90% power to reject at least 1 of the 2 null hypotheses comparing deferasirox to placebo. The sponsor took into consideration that a potential 10% of subjects would be without any post baseline LIC value, and the sample size was then increased to 52 subjects for each deferasirox group and 26 for each placebo group (that is 156 subjects in total).

Due to uncertainty about the standard deviation in LIC change from baseline at Week 52, a blinded sample size re assessment was performed when 75 % of subjects (117 subjects) had been randomised, and the result was presented to the Study Steering Committee on 13th and 14th February 2010. Based on 49 subjects with baseline and Month 6 LIC measurements, the standard deviation of absolute change from baseline was estimated to be 3.22. As this estimated standard deviation was lower than the assumed standard deviation (3.22 versus 4.00), the decision was taken that it was not necessary to increase the sample size of the study.

#### **7.1.1.8. Statistical methods**

For the efficacy analyses, LIC was measured at screening (Visit 1 or Visit 2), Week 24 (Visit 12) and Week 52 (Visit 19). The primary efficacy endpoint was the absolute change from baseline in LIC at Week 52. If no LIC measurement was available at Week 52, the last available post baseline LIC measurement before Week 52 was used. Subjects without post baseline LIC were excluded from the analyses.

The study was to be considered successful if the superiority of at least 1 deferasirox treatment group (starting dose of 5 or 10 mg/kg/day) relative to placebo could be demonstrated with regard to the primary efficacy endpoint. Analysis of covariance (ANCOVA) was performed with 1 sided t tests using Dunnett's adjustment for multiple comparisons to the placebo control group. The family wise type I error rate was set to 0.025 so that an adjusted p value of at most 0.025 would lead to rejection of the respective null hypothesis. The ANCOVA model for the change in LIC from baseline included the treatment group (5 mg/kg/day deferasirox starting dose, 10 mg/kg/day deferasirox starting dose, placebo) as factor and baseline LIC as covariate (that is the primary efficacy results were presented adjusted for baseline). In the case where both deferasirox arms were statistically superior to placebo, the 2 deferasirox groups were to be compared by means of a 2 sided t test at a significance level of 5%.

Additional supportive analysis was done by performing the primary efficacy analysis on the PPS. In a second supportive analysis, an analysis of variance (ANOVA) model was used to analyse the primary endpoint on the FAS and PPS with treatment group as the only factor. Other efficacy analyses on the primary efficacy endpoint included the number and percentage of subjects in the 2 deferasirox treatment groups and the pooled placebo group (FAS only) with an LIC decrease from baseline of at least 3 mg Fe/g dw at Week 52, or with an LIC decrease from baseline of at least 30% at Week 52. In addition, the number and percentage of subjects in the 2 deferasirox treatment groups and the pooled placebo group (FAS only) with LIC less than 3 mg Fe/g dw or less than 5 mg Fe/g dw at Week 52 were presented.

Absolute change from baseline in LIC at Week 52 was also analysed by subgroups of

- age
  - less than 18 years
  - greater than or equal to 18 years)
- gender (male, female)
- racial group
  - Caucasian
  - Asian
  - Black
  - Others
- dose increase (yes, no)
- average actual daily dose
  - greater than 0 to less than 7.5 mg/kg/day
  - 7.5 to 12.5 mg/kg/day
  - greater than 12.5 to 17.5 mg/kg/day
  - greater than 17.5 mg/kg/day
- baseline LIC
  - less than or equal to 7 mg Fe/g dw
  - greater than 7mg up to 15 mg Fe/g dw
  - greater than 15 mg Fe/g dw)
- baseline serum ferritin
  - greater than 300 to 500 µg/L
  - greater than 500 to 1000 µg/L
  - greater than 1000 µg/L), and
- splenectomy (yes, no)
- An additional ad hoc analysis was performed for absolute change from baseline in LIC at Week 52 by subgroup of underlying disease (beta thalassaemia, alpha thalassaemia, HbE beta thalassaemia).

For the secondary efficacy analyses, the secondary endpoint of change from baseline LIC at Week 24 was analysed in the same way as the primary efficacy endpoint. For the secondary endpoint of serum ferritin quarterly change from baseline, a mixed effect model was fitted for

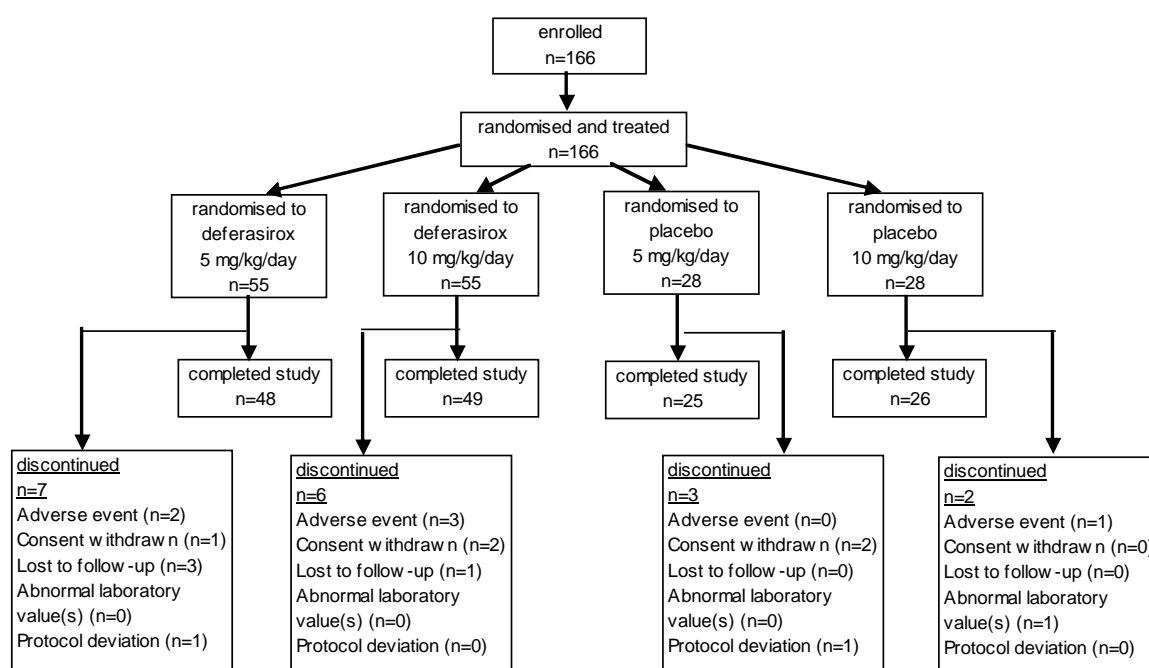
serum ferritin change (post baseline quarterly average minus baseline) with fixed factors treatment, quarter, and treatment by quarter interaction. To assess the effect of deferasirox on serum ferritin, absolute change in serum ferritin between baseline and the fourth quarter was analysed.

The secondary efficacy outcome of correlation between serum ferritin and LIC was investigated using a scatter plot. The correlation of LIC versus serum ferritin at baseline was assessed as well as the correlation of relative change in LIC versus relative change in serum ferritin at Week 24 and Week 52. The secondary efficacy outcome of effect of dose increase on efficacy was evaluated by summarising the last LIC value after the Week 24 LIC assessment and the last value before or at the Week 24 LIC assessment with descriptive statistics by treatment group and separately for subjects with and without dose increase. For the analyses of exploratory haematological and iron metabolism parameters, the observed values (and changes from baseline) at baseline, Month 3, Month 6, Month 9, Month 12 and last available month for each parameter were summarised by descriptive statistics.

#### 7.1.1.9. Participant flow

In Study A2209, a total of 166 subjects were enrolled and randomised: 55 in the deferasirox 5 mg/kg/day group, 55 in the deferasirox 10 mg/kg/day group, 28 in the placebo 5 mg/kg/day group and 28 in the placebo 10 mg/kg/day group (see Figure 1 below).

**Figure 1 Flow chart of participant flow, Study A2209**



#### 7.1.1.10. Major protocol violations/deviations

The proportions of subjects with any protocol deviations were comparable across the 2 deferasirox dose groups and the pooled placebo group (69.1% [36/55], 63.6% [35/55] and 58.9% [33/56] in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day and pooled placebo groups, respectively). The most commonly reported protocol deviations overall was 'missing auditory assessment at any visit according to evaluation schedule' (30.9% [17 out of 55], 20.0% [11 out of 55] and 19.6% [11 out of 56], respectively).

#### 7.1.1.11. Baseline data

Baseline demographic characteristics were comparable among treatment groups. The majority of subjects in each treatment group were male (52.7% [29 out of 55], 52.7% [29 out of 55], 53.6% [15 out of 28] and 57.1% [16 out of 28] in the deferasirox 5 mg/kg/day, deferasirox 10

mg/kg/day, placebo 5 mg/kg/day and placebo 10 mg/kg/day groups, respectively) and Caucasian (56.4% [31 out of 55], 54.5% [30 out of 55], 60.7% [17 out of 28] and 57.1% [16 out of 28], respectively). The mean (Standard Deviation [SD]) age was 33.1 (12.30), 31.7 (11.68), 31.9 (10.56) and 30.9 (13.88) years, respectively. Baseline mean weight was also similar among treatment groups (mean [SD] weight of 56.6 [14.23], 54.7 [12.11], 56.6 [11.20] and 55.1 [13.35] kg, respectively).

The baseline disease characteristics were comparable among treatment groups. The main underlying disease in each treatment group was beta thalassaemia (58.2% [32 out of 55], 54.5% [30 out of 55], 60.7% [17 out of 28] and 57.1% [16 out of 28], respectively), followed by HbE beta thalassaemia. The majority of subjects in each treatment group had transfusion experiences more than 6 months prior to the start of study (89.1% [49 out of 55], 90.9% [50 out of 55], 82.1% [23 out of 28] and 82.1% [23 out of 28], respectively), had no prior chelation therapy (81.8% [45 out of 55], 70.9% [39 out of 55], 60.7% [17 out of 28] and 67.9% [19 out of 28], respectively), and had no history of hepatitis (96.4% [53 out of 55], 98.2% [54 out of 55], 89.3% [25 out of 28] and 100.0% [28 out of 28], respectively). Baseline mean LIC values were comparable among the 2 deferasirox dose groups and the pooled placebo group (mean [SD] of 13.11 [7.290], 14.56 [7.925] and 15.94 [10.845] mg Fe/g dw in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day and pooled placebo groups, respectively), as was baseline mean serum ferritin values (mean [SD] of 1140.7 [804.93], 1173.9 [684.37] and 1305.1 [1017.08], respectively).

Comments: It is noted that the overall sample size of subjects less than 18 years of age was small (n=29, 17.5%; 10.9% [6 out of 55], 12.7% [7 out of 55] and 14.3% [8 out of 56] in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day, and pooled placebo groups, respectively). As the proposed additional indication is targeted towards a patient population of aged 10 years and above, the relatively small sample size of subjects less than 18 years of age may affect the ability to evaluate fully the efficacy and safety of deferasirox in the paediatric NTDT patient population aged 10 to less than 18 years, although it is noted that deferasirox is approved for use in paediatric patients aged 2 and above with transfusional iron overload. This will be discussed further in the Efficacy and Safety sections with reference to the subgroup analyses results.

#### **7.1.1.12. Results for the primary efficacy outcome**

Primary efficacy analysis showed that compared to the pooled placebo group, the decrease from baseline in LIC at Week 52 was statistically significantly greater for both the deferasirox 5 mg/kg/day group (least square means [LSMs] of absolute change of LIC from baseline of 1.95 Fe/g dw versus 0.38 Fe/g dw in the pooled placebo group,  $p=0.001$ ) and the deferasirox 10 mg/kg/day group (-3.80 Fe/g dw versus 0.38 Fe/g dw,  $p<0.001$ ). Comparison between deferasirox 5 and 10 mg/kg/day groups for the primary efficacy endpoint showed that the decrease from baseline in LIC at Week 52 was statistically significantly greater in the deferasirox 10 mg/kg/day group compared to the deferasirox 5 mg/kg/day group ( $p=0.009$ ).

As a supportive analysis, the primary efficacy analysis was carried out on the PPS, and also yielded results that were statistically significantly in favour of both the deferasirox 5 mg/kg/day group (LSMs of absolute change of LIC from baseline to Week 52 of -2.48 Fe/g dw versus 0.46 Fe/g dw in the pooled placebo group,  $p<0.001$ ) and the deferasirox 10 mg/kg/day group (-4.30 Fe/g dw versus 0.46 Fe/g dw,  $p<0.001$ ) compared to the pooled placebo group. Comparison between deferasirox 5 and 10 mg/kg/day groups for the primary efficacy endpoint on the PPS also showed that the decrease from baseline in LIC at Week 52 was statistically significantly greater in the deferasirox 10 mg/kg/day group compared to the deferasirox 5 mg/kg/day group ( $p=0.019$ ).

A second supportive analysis where an ANOVA model was fitted instead of the ANCOVA model on both the FAS and PPS yielded results which were consistent to those in the ANCOVA models.



The change from baseline in LIC at Week 52 was statistically significantly greater in both the deferasirox groups compared to the pooled placebo group, and in the deferasirox 10 mg/kg/day group compared to the deferasirox 5 mg/kg/day group.

### **7.1.1.13. Results for other efficacy outcomes**

#### **7.1.1.13.1. Other analyses on the primary efficacy endpoint**

The proportion of subjects with an LIC decrease from baseline of at least 3 mg Fe/g dw at Week 52 was greater in the deferasirox 5 mg/kg/day group compared to the pooled placebo group (32.7% [18 out of 55] versus 10.7% [6 out of 56]), and also greater in the deferasirox 10 mg/kg/day group compared to the pooled placebo group (56.4% [18 out of 55] versus 10.7% [6 out of 56]). No test of statistical significance was done. The proportion of subjects with an LIC decrease from baseline of at least 30% at Week 52 was also greater in the deferasirox 5 mg/kg/day group compared to the pooled placebo group (25.5% [14 out of 55] versus 1.8% [1 out of 56]), and also greater in the deferasirox 10 mg/kg/day group compared to the pooled placebo group (49.1% [27 out of 55] versus 1.8% [1 out of 56]). No test of statistical significance was done.

The proportion of subjects with LIC less than 5 mg Fe/g dw at Week 52 was greater in the deferasirox 5 mg/kg/day group compared to the pooled placebo group (14.5% [8 out of 55] versus 3.6% [2 out of 56]), and also greater in the deferasirox 10 mg/kg/day group compared to the pooled placebo group (27.3% [15 out of 55] versus 3.6% [2 out of 56]). The proportion of subjects with an LIC less than 3 mg Fe/g dw at Week 52 was also greater in the deferasirox 5 mg/kg/day group compared to the pooled placebo group (1.8% [1 out of 55] versus 0.0% [0 out of 56]), and also greater in the deferasirox 10 mg/kg/day group compared to the pooled placebo group (9.1% [5 out of 55] versus 0.0% [0 out of 56]).

#### **7.1.1.13.2. Subgroup analyses on the primary efficacy endpoint**

Absolute change from baseline in LIC at Week 52 was analysed by subgroups of

- age
  - less than 18 years
  - greater than or equal to 18 years)
- gender (male, female)
- racial group
  - Caucasian
  - Asian
  - Black
  - Others
- dose increase (yes, no)
- average actual daily dose
  - greater than 0 to less than 7.5 mg/kg/day
  - 7.5 to 12.5 mg/kg/day
  - greater than 12.5 to 17.5 mg/kg/day
  - greater than 17.5 mg/kg/day
- baseline LIC
  - less than or equal to 7 mg Fe/g dw

- greater than 7 up to 15 mg Fe/g dw
- greater than 15 mg Fe/g dw)
- baseline serum ferritin
  - greater than 300 to 500 µg/L
  - greater than 500 to 1000 µg/L
  - greater than 1000 µg/L), and
- splenectomy (yes, no), and
- underlying disease
  - beta thalassaemia
  - alpha thalassaemia
  - HbE beta thalassaemia

The primary endpoint was analysed by the subgroups of age, gender, race, baseline LIC categories, baseline serum ferritin categories, splenectomy and underlying disease using ANCOVA to explore the consistency of treatment effects found in the overall study population in the primary efficacy analysis. The results were consistent with the primary efficacy analysis, showing results in favour of the deferasirox 5 mg/kg/day group over the pooled placebo group across the subgroups, as well as results in favour of the deferasirox 10 mg/kg/day group over the pooled placebo group across the subgroups. The results were also in favour of the deferasirox 10 mg/kg/day group over the deferasirox 5 mg/kg/day group across the subgroups, except for the subgroup of underlying disease of alpha thalassaemia. However the sample size of this subgroup was small (n=14), making interpretation difficult.

Looking in particular at the age subgroups of less than 18 years versus greater than or equal to 18 years, the absolute change from baseline LIC at Week 52 was comparable between those aged less than 18 years and those aged greater than or equal to 18 years in the deferasirox 5 mg/kg/day group (-1.55 and -1.81 mg Fe/g dw in age groups of less than 18 years and greater than or equal to 18 years, respectively) as well as in the deferasirox 10 mg/kg/day group (-3.28 and -3.86 mg Fe/g dw, respectively).

With regards to the subgroups of subjects with and without dose increase after Week 24, results were also consistent with the primary efficacy analysis in the overall population, with greater mean LIC decrease from baseline at Week 52 in both deferasirox treatment groups compared to the pooled placebo group in both subgroups. In addition, subjects whose deferasirox dose was increased from 10 to 20 mg/kg/day had greater mean LIC decrease from baseline at Week 52 compared to subjects who were treated with 10 mg/kg/day (without dose escalation) throughout the study (-4.02 mg Fe/g dw versus -3.57 mg Fe/g dw). The mean LIC decrease from baseline at Week 52 was comparable between subjects whose deferasirox dose was increased from 5 to 10 mg/kg/day and those who were treated with 5 mg/kg/day (without dose escalation) throughout the study (-1.82 mg Fe/g dw versus -1.88 mg Fe/g dw).

With regards to the subgroups of subjects according to the average actual daily dose, results were also consistent with the primary efficacy analysis in the overall population, with greater mean LIC decrease from baseline at Week 52 in all deferasirox dose categories compared to the pooled placebo group. The mean absolute decrease in LIC from baseline at Week 52 was the greatest in subjects who received an average actual daily dose of deferasirox of greater than 12.5 to less than or equal to 17.5mg/kg/day (-4.22 mg Fe/g dw), followed by those with average actual daily dose of greater than or equal to 7.5 to less than or equal to 12.5 mg/kg/day (-3.56 mg Fe/g dw) and those with average actual daily dose of 0 to less than 7.5mg/kg/day (-1.72 mg Fe/g dw).

#### 7.1.1.13.3. Secondary efficacy analyses

Analysis of the change from baseline in LIC at Week 24 showed that there was no statistically significant difference between the deferasirox 5 mg/kg/day group and the pooled placebo group (LSMs of absolute change of LIC from baseline of -0.87 Fe/g dw versus -0.64 Fe/g dw in the pooled placebo group,  $p=0.254$ ), and between the deferasirox 10 mg/kg/day group and the pooled placebo group (-0.90 Fe/g dw versus -0.64 Fe/g dw,  $p=0.240$ ).

There was a statistically significantly greater absolute decrease in serum ferritin between baseline and the fourth quarter in the deferasirox 5 mg/kg/day group compared to the pooled placebo group (LSMs of absolute change of serum ferritin from baseline of -120.69  $\mu\text{g/L}$  versus 114.54  $\mu\text{g/L}$  in the pooled placebo group,  $p<0.001$ ), and also in the deferasirox 10 mg/kg/day group compared to the pooled placebo group (-222.00  $\mu\text{g/L}$  versus 114.54  $\mu\text{g/L}$ ,  $p<0.001$ ). The difference between the deferasirox 10 mg/kg/day group and the deferasirox 5 mg/kg/day group was not statistically significant ( $p=0.088$ ).

Analyses of the correlation of LIC versus serum ferritin showed that there was a positive correlation between baseline LIC and baseline serum ferritin ( $r=0.639$ ), as well as between change in LIC from baseline to Week 52 and change in serum ferritin from baseline to Week 52 ( $r=0.311$ ). No correlation was found between change in LIC from baseline to Week 24 and change in serum ferritin from baseline to Week 24 ( $r=0.092$ ).

Analyses on the effect on efficacy of deferasirox dose increase showed that mean absolute change in LIC between the last value before or at Week 24 and the last value after Week 24 in subjects with dose increase (from 5 to 10 mg/kg/day or 10 to 20 mg/kg/day) was greater in deferasirox treated subjects with dose increase from 10 to 20 mg/kg/day (-4.85 mg Fe/g dw) than in deferasirox treated subjects with dose increase from 5 to 10 mg/kg/day (-2.38 mg Fe/g dw). Comparing absolute change in LIC from baseline in subjects with deferasirox dose increase and those without deferasirox dose increase showed that at Week 24, subjects without dose increase had a greater mean decrease in LIC from baseline compared to those with dose increase (-2.61 mg Fe/g dw in subjects remaining on deferasirox 5 mg/kg/day versus 0.56 mg Fe/g dw in subjects with dose increase from 5 to 10 mg/kg/day; -2.48 mg Fe/g dw in subjects remaining on deferasirox 10 mg/kg/day versus 0.69 mg Fe/g dw in subjects with dose increase from 10 to 20 mg/kg/day). This is expected as only subjects without adequate decrease in LIC at Week 24 (that is those with less than 15% decrease in LIC and with LIC greater than or equal to 7 mg Fe/g dw) had their doses increased. However, by Week 52, the mean absolute change in LIC from baseline was comparable between those without dose increase and those with dose increase (-1.88 mg Fe/g dw in subjects remaining on deferasirox 5 mg/kg/day versus -1.82 mg Fe/g dw in subjects with dose increase from 5 to 10 mg/kg/day; -3.57 mg Fe/g dw in subjects remaining on deferasirox 10 mg/kg/day versus -4.02 mg Fe/g dw in subjects with dose increase from 10 to 20 mg/kg/day).

Analyses of haematological and iron metabolism parameters showed that there were no clinically significant absolute and relative changes in serum erythropoietin, absolute reticulocyte, growth differentiation factor 15, haemoglobin, plasma haemoglobin, plasma haptoglobin, lactate dehydrogenase, total serum iron, serum transferrin, transferrin saturation (calculated), soluble transferrin receptor, plasma hepcidin and labile plasma iron from baseline to the end of study across all treatment groups. There were larger decreases from baseline in median pre and post dose (2 hour post dose) non transferrin bound iron (NTBI) values in both deferasirox treatment groups compared to the placebo group. These results are consistent with the effect of deferasirox as an iron chelator.

#### 7.1.1.13.4. Other analyses

The sponsor performed additional analyses on the correlation between LIC and serum ferritin to determine whether serum ferritin can be used as a monitoring tool to predict LIC, and hence to be used as a method to monitor whether chelation treatment should be initiated, dose

escalated or interrupted, especially in countries where access to methods for determining LIC may be limited. This was done with a Receiver Operating Characteristic (ROC) analysis using data from all screened subjects with available serum ferritin and LIC values obtained before the start of treatment. In this analysis, the positive predictive value (PPV) was the proportion of subjects with high LIC in all subjects whose serum ferritin were above the serum ferritin cut off, and hence a higher PPV would indicate a better ability to predict high LIC, which could be an important metric to decide whether to initiate treatment. The negative predictive value (NPV) was the proportion of subjects with low LIC in all subjects whose serum ferritin were no greater than the serum ferritin cut off, and hence a higher NPV would indicate a better predictive ability to predict low LIC, which could be an important metric to decide whether to stop or interrupt treatment. In this study, the sponsor had used the criterion of LIC greater than or equal to 5 mg Fe/g dw to start chelation treatment (part of inclusion criteria), LIC greater than or equal to 7 mg Fe/g dw to double the dose of study treatment, and LIC less than 3 mg Fe/g dw to interrupt treatment until LIC was greater than or equal to 5 mg Fe/g dw.

The sponsor presented the conclusion that the results showed that serum ferritin greater than 800 µg/L was an adequate threshold for starting iron chelation therapy with deferasirox, as subjects with serum ferritin greater than 800 µg/L have a high probability (PPV of 92%) of having their baseline LIC greater than or equal to 5 mg Fe/g dw. With regards to the threshold to double the dose of deferasirox (LIC greater than or equal to 7 mg Fe/g dw), the sponsor presented the conclusion that serum ferritin value greater than 2000 µg/L could be considered as an adequate threshold above which subjects can be dose escalated (PPV of 93%). With regards to the threshold to interrupt or stop treatment (LIC less than 3 mg Fe/g dw), the sponsor concluded that serum ferritin value of 300 µg/L was an adequate and safe threshold to interrupt iron chelation therapy (NPV of 80%).

Comments: The sponsor, in the presentation of the results of this analysis and its conclusion, did not elaborate on the reason for selecting the particular serum ferritin levels, apart from citing the PPVs and NPVs. It is unclear to the evaluator, for example, why serum ferritin greater than 2000 µg/L had been chosen as a threshold level for predicting LIC greater than or equal to 7 mg Fe/g dw, instead of, say 1900 µg/L (PPV of 94%) or 1800 µg/L (PPV of 95%). This will be raised as a clinical question.

### **7.1.2. Other efficacy studies**

#### **7.1.2.1. Study A2202**

Study A2202 was a phase I/II open label, dose escalation multi centre<sup>8</sup> study to explore the safety and efficacy of deferasirox in patients with iron overload resulting from hereditary hemochromatosis (HH). The sponsor had provided the rationale for the study, stating that although phlebotomy is an effective treatment for the removal of iron in HH patients with iron overload, not all HH patients are eligible for phlebotomy due to underlying medical conditions (for example anaemia, heart disease), or poor venous access. Hence this study was conducted to examine the safety, tolerability and preliminary efficacy of deferasirox in HH patients with iron overload. The primary objective of the study was to explore the safety of deferasirox (dose range of 5 to 20 mg/kg/day) in adult HH patients with iron overload. The secondary objectives were to explore the effect of deferasirox on serum ferritin and to characterise the PK of deferasirox in patients with HH.<sup>9</sup> The study start date (first subject enrolled) was 23 August 2006. The study end dates (last patient completed) were 30 December 2007 and 19 March 2009 for the core study and the extension phase, respectively.

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<sup>8</sup> Study A2202 was conducted in 17 centres across 6 countries: Australia (1 centre), Canada (1 centre), Germany (4 centres), France (1 centre), Italy (2 centres) and the United States (8 centres).

<sup>9</sup> The sponsor had stated that as this was a dose-escalation study, the sample size had not been determined to power the efficacy analyses, and hence all the efficacy results in this study were to be considered exploratory in nature.

The study involved 4 planned dose levels: 5 mg/kg/day (dose level 1), 10 mg/kg/day (dose level 2), 15 mg/kg/day (dose level 3) and 20 mg/kg/day (dose level 4).<sup>10</sup> At least 40 subjects were planned to be treated, to give at least 8 evaluable subjects per dose level. Subjects were to receive treatment for 24 weeks in the core study and an additional 6 months in the extension phase. Treatment was to be withheld if serum ferritin fell to less than 100 µg/L, until the serum ferritin was greater than 300 µg/L when the study drug could be restarted at the same dose. Subjects were stratified at enrolment by serum ferritin levels (at the screening visit) into 2 strata: serum ferritin between 300 to 600 µg/L or greater than 600 µg/L to 1500 µg/L. Enrolment into dose levels 2, 3 and 4 was staggered based on the data generated from the previous dose level, but separately by stratum. The study clinical team and the study Independent Safety Monitoring Committee (SMC) performed a safety review for each dose level once the 6th patient enrolled in that level had been treated for 4 weeks. Dose escalation was to be continued until dose level 4 was reached or review of the safety data indicated a need to expand the current dose level, titrate the dose downward or stop the trial.<sup>11</sup> In the extension phase, the subjects received deferasirox at the same dose that they had been assigned to in the core study. During the extension phase, the dose of deferasirox could be increased by 5 mg/kg/day to the highest tolerated dose found in the core study in subjects with serum ferritin greater than 100 µg/L, had less than 10 % decrease in serum ferritin over a 2 month period, or had an increase above baseline ferritin level on 2 consecutive visits.

Subjects enrolled in the core study were male or female adult subjects greater than or equal to 18 years of age who were homozygous for the C282Y mutation (as documented by molecular diagnostic testing), who had serum ferritin values greater than or equal to 300 µg/L and less than or equal to 2000 µg/L and with transferrin saturation greater than or equal to 45%. Subjects who had iron overload not due to hereditary hemochromatosis, any interfering disease, treatment with phlebotomy within 2 weeks of screening visit, desferal treatment within one month of screening visit, blood transfusion during the 6 months prior to study entry, or low haemoglobin levels (males: less than 13 mg/dL; females: less than 12 mg/dL) were excluded. Subjects who had completed the core study successfully and had demonstrated compliance with visits, procedures and study drug administration during the core study were eligible to enter the extension phase. Subjects with unacceptable toxicity to deferasirox during the core study were excluded from the extension phase.

The main efficacy variable was the effect of deferasirox on serum ferritin by assessing the change in serum ferritin from baseline at Weeks 24 and 48. The secondary efficacy variables included further characterisation of the effect of deferasirox on serum ferritin (longitudinal course and time to normalisation) and characterisation of the PK of deferasirox. The longitudinal analysis on the serum ferritin time profile was done by a linear mixed effects model for serum ferritin with patient as a random effect, visit and dose cohort as fixed effects, and baseline serum ferritin as a continuous covariate. Four analysis sets were defined in the study. The safety population included all subjects who had received at least one dose of study drug within the core study and had at least one safety assessment within the core study. The per protocol (PP) population included all subjects of the safety population who did not have any major protocol deviation. The extension safety population included all subjects who had received at least one dose of study drug within the extension phase and had at least one safety assessment within the extension phase. The extension PP population included all subjects of the PP population who also were part of the extension safety population.

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<sup>10</sup> The sponsor had provided the rationale for the dose selection, stating that the mean baseline iron burden in patients with HH was approximately 6 to 7g, and that from the studies in patients with transfusional iron overload, the calculated mean efficiency for daily iron removal was 0.021 mg Fe/kg per mg/kg of deferasirox. As deferasirox had not previously been tested in HH patients, a dose range of 5 to 20 mg/kg had been selected in order to be able to evaluate annual iron removal below and above the 6 to 7 g range.

<sup>11</sup> In the actual study conduct, the 20 mg/kg/day dose level was not explored as 15 mg/kg/day was judged to be the highest tolerable dose by clinical review.

Forty nine subjects were enrolled into the study (11, 15 and 23 subjects in the 5, 10 and 15 mg/kg/day dose level cohorts, respectively), out of which 37 completed the core study (10, 11 and 16 subjects in the 5, 10 and 15 mg/kg/day dose level cohorts, respectively). The majority of the discontinuations were due to adverse events (7 out of 49, 14.3%) and were in the 10 and 15 mg/kg/day dose level cohorts. Out of the 37 subjects who completed the core study, 26 (9, 6 and 11 subjects in the 5, 10 and 15 mg/kg/day dose level cohorts, respectively) chose to continue with the extension study and 23 completed the extension study (9, 6 and 8 subjects in the 5, 10 and 15 mg/kg/day dose level cohorts, respectively). Out of the 3 discontinuations, 2 were due to adverse events and 1 due to administrative problems (non compliance with study). All 49 subjects were included in the safety population. Out of these 49 subjects, 1 subject was excluded from the PP population for having clinical evidence of active hepatitis B or C. All 26 subjects who entered the extension phase were included in the extension safety population and the extension PP population.

All subjects were Caucasian. The majority were male (81.8% [9 out of 11], 73.3% [11 out of 15] and 56.5% [13 out of 23] in the 5, 10 and 15 mg/kg/day dose cohorts, respectively). Mean (SD) age was 55.8 (12.78), 47.8 (10.26), and 49.8 (16.41) years, respectively, and mean (SD) BMI was 28.93 (2.204), 27.18 (6.366), and 26.29 (5.296) kg/m<sup>2</sup>, respectively. Mean time since initial diagnosis of HH was longer in the 5 mg/kg/day dose cohort (6.6 years) compared to in the 10 mg/kg/day (1.3 years) and the 15 mg/kg/day (2.6 years) dose cohorts. Mean baseline serum ferritin was higher in the 10 mg/kg/day dose cohort (926.7 µg/L) compared to in the 15 mg/kg/day dose cohort (797.4 µg/L) and the 5 mg/kg/day dose cohort (636.7 µg/L).

Efficacy analyses showed that there was a decrease in serum ferritin from baseline at Week 24 (that is, the end of core study) at all three dose levels, but the within cohort variation was large, likely due to the small sample size. The mean (SD) change in serum ferritin from baseline at Week 24 was greater in the 10 and 15 mg/kg/day dose cohorts (-356.5 [321.09] µg/L and -320.6 [309.49] µg/L, respectively), compared to the 5 mg/kg/day dose cohort (-159.9 [275.43] µg/L). There was also a decrease in serum ferritin from baseline at Week 48 (that is, end of extension phase) at all three dose levels, but again the within cohort variation was large. The mean (SD) change in serum ferritin from baseline at Week 48 in the per protocol population was greater in the 10 and 15 mg/kg/day dose cohorts (-610.5 [341.84] µg/L and -571.6 [552.81] µg/L, respectively), compared to the 5 mg/kg/day dose cohort (-389.1 [185.35] µg/L).

The longitudinal analysis of serum ferritin from baseline to end of core study (that is, Week 24) showed that when controlling baseline levels and visit time, the serum ferritin level of the 5 mg/kg/day cohort was statistically significantly higher than that of the 15 mg/kg/day cohort (mean difference of 159.7 µg/L, p=0.029). The higher serum ferritin values in the 5 mg/kg/day cohort compared to the 10 mg/kg/day cohort (mean difference of 127.1 µg/L, p=0.109) and in the 10 mg/kg/day cohort compared to the 15 mg/kg/day cohort (mean difference 32.5 µg/L, p=0.613) were not statistically significant. The longitudinal analysis of serum ferritin from baseline to end of extension study (that is, Week 48) showed that when controlling baseline levels and visit time, the serum ferritin level of the 5 mg/kg/day cohort was statistically significantly higher than that of the 10 mg/kg/day cohort (mean difference of 125.5 µg/L, p=0.048) and that of the 15 mg/kg/day cohort (mean difference of 201.6 µg/L, p<0.001). The higher serum ferritin value in the 10 mg/kg/day compared to that in 15 mg/kg/day was not statistically significant (mean difference of 76.1 µg/L, p =0.197).

In the analyses of time to normalisation of serum ferritin, “normalisation” was defined as a serum ferritin value less than 100 µg/L. In the core study, the proportion of subjects with serum ferritin normalisation was low (0.0% [0 out of 11], 13.3% [2 out of 15] and 22.7% [5 out of 22] in the 5, 10 and 15 mg/kg/day cohorts, respectively). The median duration of serum ferritin normalisation was 14.0 and 73.0 days for the 10 and 15 mg/kg/day cohorts, respectively. The median time to normalisation was not estimable due to the low incidences of normalisation. In the core plus extension study analyses (on the PP population), the proportion of subjects with

serum ferritin normalisation was 36.4% [4 out of 11], 13.3% [2 out of 15] and 36.4% [8 out of 22] in the 5, 10 and 15 mg/kg/day cohorts, respectively). Two of the subjects in the 5 mg/kg/day group had normalised serum ferritin only after dose escalation to 10 mg/kg/day. The median duration of serum ferritin normalisation was 29.5, 14.0 and 45.5 days for the 5, 10 and 15 mg/kg/day cohorts, respectively. The median time to normalisation of serum ferritin was 358 and 341 days for the 5 and 15 mg/kg/day cohorts, respectively. The median time to normalisation was not estimable in 10 mg/kg/day cohort due to the low incidence of normalisation.

PK analyses in the core study showed that steady state PK of deferasirox was achieved by week 4 in all 3 dose levels cohorts. Trough concentrations of deferasirox over 24 weeks showed no accumulation after multiple dosing up to 24 week of treatment. Mean trough concentrations were approximately dose proportional from 5 to 15 mg/kg/day at Week 4. This dose proportionate trend continued between the 5 and 10 mg/kg/day dose levels up to Week 24, but was diminished from Weeks 8 to 24 between the 10 and 15 mg/kg/day cohorts.

Comments: The primary objective of the study was to explore the safety of deferasirox (dose range of 5 to 20 mg/kg/day) in adult HH patients with iron overload, and the efficacy analyses were exploratory. In addition, the small sample size makes meaningful interpretation difficult. Overall, the study design, inclusion and exclusion criteria and efficacy endpoints were appropriate. Analysis in the per protocol population, which excludes subjects with major protocol deviations, is acceptable in an exploratory efficacy study where the objective is to explore the pharmacological effect of a new drug in an ideal study population who could adhere to the study conditions, including dosing regimen.

Efficacy analyses in this study showed that there were decreases in serum ferritin from baseline at Weeks 24 and 48 in all 3 dose cohorts. At both timepoints, there were greater decreases from baseline in the 10 and 15 mg/kg/day cohorts compared to the 5 mg/kg/day cohort. The longitudinal analysis of serum ferritin from baseline to end of Weeks 24 and 48 showed that the differences in serum ferritin between the 10 and 15 mg/kg/day dose cohorts at both time points were not statistically significant. The difference in serum ferritin between the 5 and 10 mg/kg/day dose cohorts was not statistically significant at Week 24, but was statistically significant (higher in the 5 mg/kg/day cohort compared to the 10 mg/kg/day cohort) at Week 48. The difference in serum ferritin between the 5 and 15 mg/kg/day dose cohorts was statistically significant (higher in the 5 mg/kg/day cohort compared to the 15 mg/kg/day cohort) at both Weeks 24 and 48.

Overall, evaluation of the efficacy results of this study did not yield any findings or concerns relevant to the current submission. The sponsor is not proposing to extend an indication for deferasirox involving patients with HH, and is also not proposing any changes to the existing PI based on the results of this study.

#### **7.1.2.2. Analyses performed across trials (pooled analyses and meta analyses)**

Not applicable.

## **7.2. Evaluator's conclusions on clinical efficacy**

Overall, the efficacy study results of the pivotal study (A2209) are supportive of the efficacy claim for the use of deferasirox in the treatment of chronic iron overload in patients with NTDT. The study design, study inclusion and exclusion criteria, and study endpoints were appropriate. The primary and secondary endpoints of the study allowed evaluation of the effect of deferasirox on change from baseline in LIC after 52 weeks of treatment (primary endpoint) and after 24 weeks of treatment, effect of deferasirox on serum ferritin, as well as exploration of the

efficacy of dose doubling of deferasirox and correlation between serum ferritin and LIC. The efficacy endpoints did not include evaluation of effect on survival, relief of symptoms or end organ damage arising from chronic iron overload. However, although there are no established guidelines regarding appropriate study endpoints for iron chelators, it is noted by the evaluator that the currently approved indication for Exjade in patients with transfusional overload was based on studies with LIC as endpoints (as presented in the currently approved PI for Exjade). The baseline demographic and disease characteristics of the study population were comparable across treatment groups.

Primary efficacy outcome analysis showed that compared to the pooled placebo group, the decrease from baseline in LIC at Week 52 was statistically significantly greater in both the deferasirox 5 mg/kg/day group (-1.95 Fe/g dw versus 0.38 Fe/g dw in the pooled placebo group,  $p=0.001$ ) and the deferasirox 10 mg/kg/day group (-3.80 Fe/g dw versus 0.38 Fe/g dw,  $p<0.001$ ). Comparison between deferasirox 5 mg/kg/day and deferasirox 10 mg/kg/day for the primary efficacy endpoint showed that the decrease from baseline in LIC at Week 52 was statistically significantly greater in the deferasirox 10 mg/kg/day group compared to the deferasirox 5 mg/kg/day group ( $p=0.009$ ). Supportive analyses of the primary efficacy outcome on the PPS, and by using an ANOVA model instead of the ANCOVA model, yielded similar results. Subgroup analyses on the primary efficacy outcome also yielded results consistent with the analysis in the overall population. However, analyses of the change in LIC from baseline at Week 24 showed no statistically significant difference between either deferasirox dose groups and the pooled placebo group.

Analyses of the effect of deferasirox on serum ferritin showed there was also a statistically significantly greater absolute decrease in serum ferritin between baseline and the fourth quarter in the deferasirox 5 mg/kg/day group compared to the pooled placebo group (-120.69  $\mu\text{g/L}$  versus 114.54  $\mu\text{g/L}$ ,  $p<0.001$ ), and also in the deferasirox 10 mg/kg/day group compared to the pooled placebo group (-222.00  $\mu\text{g/L}$  versus 114.54  $\mu\text{g/L}$ ,  $p<0.001$ ). However, the difference between the deferasirox 10 and 5 mg/kg/day groups was not statistically significant ( $p=0.088$ ).

The proposed additional indication is targeted towards a patient population of aged 10 years and above, and hence includes the paediatric NTDT patient population aged 10 to less than 18 years. In the subgroup analyses on the primary efficacy outcome, looking in particular at the age subgroups of less than 18 years versus greater than or equal to 18 years, it is noted that the overall sample size of subjects less than 18 years of age was small ( $n=29$ , 17.5%; 10.9% [6 out of 55], 12.7% [7 out of 55] and 14.3% [8 out of 56] in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day, and pooled placebo groups, respectively). Efficacy analyses results with reference to the absolute change from baseline in LIC at Week 52, were comparable between the paediatric subgroup (aged less than 18 years) and those greater than or equal to 18 years in the deferasirox 5 mg/kg/day group (-1.55 and -1.81 mg Fe/g dw in age groups of less than 18 years and greater than or equal to 18 years, respectively) as well as in the deferasirox 10 mg/kg/day group (-3.28 and -3.86 mg Fe/g dw, respectively).

Although 2 starting doses of deferasirox were tested in this study, the recommended starting dose in NTDT patients in the proposed PI was deferasirox 10 mg/kg/day. The sponsor had provided a summary of the analyses of the mean changes from baseline in LIC and serum ferritin at Week 52, by the actual average daily dose of deferasirox administered to the subjects during the study, and results showed that there was a dose response effect in these efficacy endpoints. During the study, the proportion of subjects who needed to have dose escalation due to suboptimal response (that is those with less than 15% decrease in LIC and with LIC greater than or equal to 7 mg Fe/g dw) at Week 24, was comparable between the 5 mg/kg/day (47.3%, 26 out of 55) and 10 mg/kg/day groups (45.5%, 25 out of 55). However, among subjects who did not need dose escalation at Week 24, those who remained on 5 mg/kg/day of deferasirox had smaller decrease from baseline in LIC at Week 52 (change from baseline of -1.88 Fe/g dw)



compared to at Week 24 (change from baseline of -2.61 Fe/g dw). In contrast, subjects who remained on 10 mg/kg/day of deferasirox had further decrease from baseline in LIC at Week 52 (change from baseline of -3.57 Fe/g dw) compared to at Week 24 (change from baseline of -2.48 Fe/g dw). Among subjects who needed and had dose escalation at Week 24, analyses of the mean absolute change in LIC between the last value before or at Week 24 and that after Week 24 showed that there was a greater change in deferasirox treated subjects with dose increase from 10 to 20 mg/kg/day (-4.85 mg Fe/g dw) than in deferasirox treated subjects with dose increase from 5 to 10 mg/kg/day (-2.38 mg Fe/g dw). Overall, by Week 52, the proportion of subjects with an LIC decrease from baseline of at least 3 mg Fe/g dw was 56.4% in the deferasirox 10 mg/kg/day group compared with 32.7% in the deferasirox 5 mg/kg/day group, and the proportion of subjects with an LIC decrease from baseline of at least 30% was 49.1% in the deferasirox 10 mg/kg/day group compared with 25.5% in the deferasirox 5 mg/kg/day group. By Week 52, the proportion of subjects with LIC less than 5 mg Fe/g dw or less than 3 mg Fe/g dw was 27.3% and 9.1%, respectively, in the deferasirox 10 mg/kg/day group, compared with 14.5% and 1.8%, respectively, in the deferasirox 5 mg/kg/day group. A complete evaluation of the appropriateness of the proposed starting dose of deferasirox 10 mg/kg/day instead of 5 mg/kg/day will also depend on the safety profile of the 2 doses of deferasirox, and a weighing of the benefit risk profiles of the 2 doses.

With regards to the efficacy of dose doubling, results suggested a positive effect on efficacy with dose doubling. At Week 24, subjects without dose increase had a greater mean decrease in LIC from baseline compared to those with dose increase,<sup>12</sup> as is expected since only subjects without adequate decrease in LIC at Week 24 had their doses increased. However, by Week 52, the mean absolute change in LIC from baseline was comparable between those without dose increase and those with dose increase.<sup>13</sup>

## 8. Clinical safety

### 8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

#### Pivotal efficacy study

In the pivotal efficacy study A2209, the following safety data were collected:

- General adverse events (AEs) were assessed by the investigator obtaining and recording all AEs at each scheduled visit.
- AEs of particular interest were analysed based on safety findings observed during previous clinical studies of deferasirox in patients with transfusional iron overload. Nine groups of AEs of special interest were defined: increased serum creatinine; renal tubular disorders; acute renal failure; increased liver transaminases; hepatic failure; hearing loss; lens opacities, retinal changes and optic neuritis; GI haemorrhage and ulcers, esophagitis; peripheral blood cytopenias. The sponsor had stated that these AEs of special interest corresponded to the identified potential risks in the Risk Management Plan.

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<sup>12</sup> Absolute change in LIC from baseline of -2.61 mg Fe/g dw in subjects remaining on deferasirox 5 mg/kg/day versus 0.56 mg Fe/g dw in subjects with dose increase from 5 to 10 mg/kg/day; absolute change in LIC from baseline of -2.48 mg Fe/g dw in subjects remaining on deferasirox 10 mg/kg/day versus 0.69 mg Fe/g dw in subjects with dose increase from 10 to 20 mg/kg/day.

<sup>13</sup> Absolute change in LIC from baseline of -1.88 mg Fe/g dw in subjects remaining on deferasirox 5 mg/kg/day versus -1.82 mg Fe/g dw in subjects with dose increase from 5 to 10 mg/kg/day; absolute change in LIC from baseline of -3.57 mg Fe/g dw in subjects remaining on deferasirox 10 mg/kg/day versus -4.02 mg Fe/g dw in subjects with dose increase from 10 to 20 mg/kg/day

- Auditory and ophthalmologic examinations<sup>14</sup> were performed during screening and after 12 months (that is, Week 52). Significant findings of the auditory and ophthalmologic examinations that met the definition of an AE were to be reported as an AE.
- Laboratory tests performed included haematology, blood chemistry (alkaline phosphatase [ALP], albumin, gamma-glutamyl transpeptidase [GGT], aspartate aminotransferase (AST), alanine aminotransferase (ALT), total and fractionated bilirubin, total protein, serum potassium, sodium, chloride, creatinine, blood urea nitrogen (BUN), glucose, calcium, inorganic phosphorus, uric acid, C-reactive protein) and urinalysis.
- Other safety endpoints included vital signs, 12 lead electrocardiogram (ECG) and echocardiography.

#### **8.1.1. Pivotal studies that assessed safety as a primary outcome**

Not applicable.

#### **8.1.2. Dose response and non-pivotal efficacy studies**

The non pivotal efficacy study A2202, conducted in patients with HH, provided safety data, as follows:

- adverse events, vital signs, routine laboratory evaluations, 12 lead ECG, and auditory and ophthalmologic examinations.

#### **Other studies evaluable for safety only**

Not applicable.

### **8.2. Pivotal studies that assessed safety as a primary outcome**

Not applicable.

### **8.3. Patient exposure**

In Study A2209, the duration of exposure was comparable among the treatment groups. The mean duration of exposure was 11.4 to 11.8 months across treatment groups. The majority of subjects had at least 9 months of exposure (89.1% of subjects in each deferasirox group, and 94.6% of subjects in the pooled placebo group). The duration of exposure was also comparable across average actual daily dose categories. The mean duration of exposure was 11.1 to 12.3 months across the dose categories. The majority of subjects across the dose categories had at least 9 months of exposure (84.9% to 100%).

In Study A2202, the overall mean duration of exposure in the core study was 18.3 weeks, and was comparable between the 5 mg/kg/day group (22.2 weeks) and the 10 mg/kg/day group (19.0 weeks). The mean duration of exposure was shorter in the 15 mg/kg/day group (15.9 weeks). The overall mean duration of exposure in the core plus extension study<sup>15</sup> was 40.4 weeks, and was comparable between the 5 mg/kg/day group (43.4 weeks) and the 10 mg/kg/day group (48.4 weeks). The mean duration of exposure was shorter in the 15 mg/kg/day group (33.6 weeks).

Comments: Overall, the study drug exposure is adequate to assess the safety profile of deferasirox in patients with NTDT.

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<sup>14</sup> The ophthalmologic examination included visual acuity test, tonometry, slit lamp examination of anterior segment, and slit lamp examination of the lens.

<sup>15</sup> In the safety section of this evaluation report, the term "core plus extension study" is used to denote analyses in the extension safety population set, unless otherwise specified.

## **8.4. Adverse events**

### **8.4.1. All adverse events (irrespective of relationship to study treatment)**

#### **8.4.1.1. Pivotal study**

Overall, the percentages of subjects with any AEs were comparable among treatment groups (76.4% [42 out of 55], 78.2% [43 out of 55], and 80.4% (45 out of 56) in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day, and pooled placebo groups, respectively).

The most commonly reported AEs in the deferasirox 5 mg/kg/day group were upper respiratory tract infection (12.7%, 14.5% and 19.6% in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day, and pooled placebo groups, respectively) and pyrexia (10.9%, 10.9% and 14.3%, respectively). The most commonly reported AEs in the deferasirox 10 mg/kg/day group were headache (3.6%, 16.4% and 14.3% in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day, and pooled placebo groups, respectively) and upper respiratory tract infection. AEs that occurred at higher incidence in both deferasirox groups compared to the pooled placebo group were oropharyngeal pain (7.3%, 10.9% and 3.6%, respectively), anaemia (5.5%, 7.3%, and 3.6%, respectively), upper abdominal pain (5.5%, 5.5% and 0.0%, respectively), and influenza (5.5%, 5.5% and 1.8%, respectively).

#### **8.4.1.2. Other studies**

##### **8.4.1.2.1. Study A2202 core study**

Overall, the percentages of subjects with any AEs were comparable among treatment groups (90.9% (10 out of 11), 93.3% (14 out of 15), and 100.0% (23 out of 23) in the deferasirox 5, 10 and 15 mg/kg/day groups, respectively). Overall, the most commonly reported AEs were diarrhoea (18.2%, 40.0% and 43.5% in the deferasirox 5, 10 and 15 mg/kg/day groups, respectively) and headache (9.1%, 13.3% and 30.4%, respectively).

##### **8.4.1.2.2. Study A2202 core plus extension study**

Overall, the percentages of subjects with any AEs were comparable among treatment groups (100.0% [9 out of 9], 83.3% [5 out of 6], and 100.0% [11 out of 11] in the deferasirox 5, 10 and 15 mg/kg/day groups, respectively). Overall, the most commonly reported AE was diarrhoea (22.2%, 16.7% and 36.4% in the deferasirox 5, 10 and 15 mg/kg/day groups, respectively).

### **8.4.2. Treatment related adverse events (adverse drug reactions)**

#### **8.4.2.1. Pivotal study**

Overall, the percentages of subjects with any treatment related AEs were higher in the deferasirox 5 and 10 mg/kg/day groups (23.6% [13 out of 55] and 32.7% [18 out of 55], respectively) compared to the pooled placebo group (16.1% [9 out of 56]). The most commonly reported treatment related AEs in the deferasirox 5 mg/kg/day group was nausea (5.5%, 7.3% and 7.1% in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day, and pooled placebo groups, respectively). The most commonly reported AEs in the deferasirox 10 mg/kg/day group were diarrhoea (0.0%, 9.1% and 1.8% in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day, and pooled placebo groups, respectively) and rash (3.6%, 9.1% and 1.8%, respectively).

#### **8.4.2.2. Other studies**

##### **8.4.2.2.1. Study A2202 core study**

Overall, the percentages of subjects with any treatment related AEs were higher in the deferasirox 10 and 15 mg/kg/day groups (73.3% [11 out of 15] and 87.0% [20 out of 23], respectively) compared to the deferasirox 5 mg/kg/day group (36.4% [4 out of 11]). Overall, the most commonly reported treatment related AEs were diarrhoea (9.1%, 26.7% and 39.1% in

the deferasirox 5, 10 and 15 mg/kg/day groups, respectively) and blood creatinine increased (0.0%, 20.0% and 17.4%, respectively).

#### **8.4.2.2.2. Study A2202 core plus extension study**

Overall, the percentages of subjects with any treatment related AEs were higher in the deferasirox 15 mg/kg/day groups (90.9% [10 out of 11]) compared to the deferasirox 5 and 10 mg/kg/day groups (55.6% [5 out of 9] and 50.0% [3 out of 6], respectively). Overall, the most commonly reported treatment related AEs were diarrhoea (11.1%, 16.7% and 36.4% in the deferasirox 5, 10 and 15 mg/kg/day groups, respectively) and blood creatinine increased (11.1%, 33.3% and 27.3%, respectively).

### **8.4.3. Deaths and other serious adverse events**

#### **8.4.3.1. Pivotal study**

There were no deaths during the study. The overall incidence of Serious Adverse Events (SAEs) was comparable among treatment groups (12.7% [7 out of 55], 16.4% [9 out of 55], and 14.3% [8 out of 56] in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day, and pooled placebo groups, respectively). SAEs that were reported in at least 2 subjects in either deferasirox group were pyrexia (1.8% [1 out of 55], 5.5% [3 out of 55] and 0.0% [0 out of 56] in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day, and pooled placebo groups, respectively) and anaemia (1.8% [1 out of 55], 3.6% [2 out of 55] and 0.0% [0 out of 56], respectively). Other preferred terms were reported for only one subject each in either deferasirox group.

SAEs that were considered related to study drug were reported for 4 subjects, of which 3 were in the deferasirox 5 mg/kg/day group, and 1 in the deferasirox 10 mg/kg/day group. One subject in the deferasirox 5 mg/kg/day group (38 year old male) had right abdominal pain (severe) on Day 138 and was hospitalised. Ultrasonography of abdomen revealed microcholelithiasis of the gallbladder, but the investigator had judged that the microcholelithiasis was not the cause of the event (abdominal pain) but an incidental finding. No action was taken with the study medication. The SAE was resolved on Day 140 and the subject completed the core (double blind) study and continued into the open label extension study. Another subject in the deferasirox 5 mg/kg/day group with treatment related SAE was a 48 year old male who experienced cellulitis (exacerbation of chronic leg ulcer with cellulitis) (severe) on Day 240. No action was taken with the study medication. The SAE was resolved on Day 303 and the subject completed the core study and continued into the extension study. The third subject in the deferasirox 5 mg/kg/day group with treatment related SAE was a 26 year old female who had liver toxicity reported as an SAE on Day 382. The actual daily dose was 5.7 mg/kg/day at the time of event onset. She was hospitalised and study medication was temporarily interrupted on Day 383 till Day 395. There were no clinical laboratory values available for the SAE period (last value Day 326) as the patient was hospitalised outside the investigational site. The patient completed the core study with the event ongoing. The subject in the deferasirox 10 mg/kg/day group with treatment related SAE was a 41 year old male who reported pruritus and rash as SAEs on Day 21 (resulting in hospitalisation) and pyrexia as an SAE Day 22. Study medication was temporarily interrupted due to these SAEs events till Day 56. Pruritus and rash resolved on Day 57, and pyrexia resolved on Day 28. Study medication was restarted at a reduced dose of 5 mg/kg/day on Day 57, but later permanently discontinued due to recurrence of pruritus and rash on Day 58.

#### **8.4.4. Other studies**

##### **8.4.4.1. Study A2202 core study**

There were no deaths or SAEs reported during the core study.

#### **8.4.4.2. Study A2202 core plus extension study**

There were no deaths during the extension study. One SAE (“prostate cancer recurrent”) was reported in the extension study in the 5 mg/kg/day group. The subject in question had a history of prostate cancer and prostatectomy, and was diagnosed with recurrence of prostate cancer. The event was not considered related to study drug.

#### **8.4.5. Discontinuation due to adverse events**

##### **8.4.5.1. Pivotal studies**

The overall incidence of AEs leading to permanent discontinuation of study drug was low and comparable among treatment groups (5.5% [3 out of 55], 5.5% [3 out of 55], and 3.6% [2 out of 56] in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day, and pooled placebo groups, respectively).

##### **8.4.5.2. Other studies**

###### **8.4.5.2.1. Study A2202 core study**

The incidence of AEs leading to discontinuation of study drug was comparable between the deferasirox 10 and the 15 mg/kg/day group (20.0% [3 out of 15] and 21.7% [5 out of 23], respectively). There were no AEs that led to discontinuation in the deferasirox 5 mg/kg/day group.

###### **8.4.5.2.2. Study A2202 core plus extension study**

AEs leading discontinuations were reported in 2 subjects (both in the deferasirox 15 mg/kg/day group) in the core plus extension study, 1 due to diarrhoea, and the other due to increased transaminases.

#### **8.5. Laboratory tests**

In Study A2209, the incidence of pre specified notably abnormal values in post baseline key safety laboratory parameters was low across the treatment groups. Higher incidences in either deferasirox group compared to the pooled placebo group occurred with notably abnormal serum creatinine<sup>16</sup> (0.0%, 5.5% [3 out of 55] and 0.0% in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day, and pooled placebo groups, respectively), creatinine clearance<sup>17</sup> (1.8% [1 out of 55], 1.8% [1 out of 55] and 0.0%, respectively), and urinary protein/creatinine ratio (UPCR)<sup>18</sup> (1.8% [1 out of 55], 0.0% and 0.0%, respectively).

##### **8.5.1. Liver function**

###### **8.5.1.1. Pivotal study**

The majority of subjects in each treatment group had ALT and AST values within normal range at baseline and remained within the normal range throughout the study duration (ALT: 67.5%, 70.0% and 60.0% in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day, and pooled placebo groups, respectively; AST: 76.3%, 63.2% and 60.0%, respectively). The proportion of subjects with a shift to a maximum post baseline ALT of greater than 2.5 times the upper limit of normal (ULN) (that is, Grade 2 and above) from a baseline ALT of lower grades was higher in the deferasirox 10 mg/kg/day group (10.9%; 6 out of 55) compared to the deferasirox 5 mg/kg/day (7.3%; 4 out of 55) and the pooled placebo group (5.4%; 3 out of 56). The

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<sup>16</sup> Notably abnormal serum creatinine was defined as serum creatinine greater than 33% increase from baseline and greater than ULN at greater than or equal to 2 consecutive post-baseline values

<sup>17</sup> Notably abnormal creatinine clearance was defined as creatinine clearance less than 60 mL/min at greater than or equal to 2 consecutive post-baseline values

<sup>18</sup> Notably abnormal UPCR was defined as value of greater than or equal to 1.0 mg/mg at 2 or more consecutive post-baseline values

proportion of subjects with a shift to a maximum post baseline AST of greater than 2.5 times ULN (that is, Grade 2 and above) from a baseline AST of lower grades was comparable among treatment groups (5.5% [3 out of 55], 3.6% [2 out of 55] and 7.1% [4 out of 56] in the deferasirox 10 mg/kg/day group, deferasirox 5 mg/kg/day, and the pooled placebo group, respectively).

Two subjects had notably abnormal transaminase values (defined as AST or ALT values of greater than 5 times ULN and greater than 2 times baseline). One subject in the deferasirox 10 mg/kg/day group had an AST value that met the criteria of notable abnormality. The other subject was in the 10 mg/kg/day placebo group and had AST and ALT values that met the criteria of notable abnormality.

Over time from baseline to Month 12, mean ALT decreased from 34.1 U/L at baseline to 23.0 U/L at Month 12 (mean change from baseline of -11.3 U/L) in the deferasirox 10 mg/kg/day group. Change from baseline in mean ALT at Month 12 was minimal in the deferasirox 5 mg/kg/day group (-2.1 U/L) and the pooled placebo group (-2.4 U/L). Mean AST decreased from 37.9 U/L at baseline to 31.6 U/L at Month 12 (mean change from baseline of -5.4 U/L) in the deferasirox 10 mg/kg/day group. Change from baseline in mean AST at Month 12 was minimal in the deferasirox 5 mg/kg/day group (-1.8 U/L) and the pooled placebo group (0.8 U/L).

### **8.5.1.2. Other studies**

#### **8.5.1.2.1. Study A2202 core study**

There were no subjects with post baseline ALT or AST greater than 10 times ULN, or AST greater than 5 times ULN in the core study. Three subjects (all in the 15 mg/kg/day group) had ALT greater than 5 times ULN, one of whom had ALT greater than 5 times ULN on 2 consecutive measurements. The proportion of subjects with a shift to any post baseline ALT of greater than ULN from a normal baseline ALT was lower in the deferasirox 5 mg/kg/day group (9.1%; 1 out of 11) compared to the 10 mg/kg/day group (33.3%; 5 out of 15) and the 15 mg/kg/day group (39.1%; 9 out of 23). The proportion of subjects with a shift to any post baseline AST of greater than ULN from a normal baseline AST was comparable between the deferasirox 10 mg/kg/day group (40.0%; 6 out of 15) and the 15 mg/kg/day group (39.1%; 9 out of 23). There were no subjects in the deferasirox 5 mg/kg/day group who had a shift to any post baseline AST of greater than ULN from a normal baseline AST.

#### **8.5.1.2.2. Study A2202 core plus extension study**

There were no subjects with post baseline ALT or AST greater than 10 times ULN, or AST greater than 5 times ULN in the core plus extension study. One subject (in the 15 mg/kg/day group) had ALT greater than 5 times ULN which had occurred already in the core study (that is there were no additional subjects with ALT greater than 5 times ULN during the extension). The proportions of subjects with a shift to any post baseline ALT of greater than ULN from a normal baseline ALT were 22.2% (2 out of 9), 16.7% (1 out of 6), and 27.3% (3 out of 11) in the deferasirox 5, 10 and 15 mg/kg/day groups, respectively. The proportions of subjects with a shift to any post baseline AST of greater than ULN from a normal baseline AST were 11.1% (1 out of 9), 16.7% (1 out of 6), and 45.5% (5 out of 11), respectively.

Over time from baseline to Week 48, the proportion of subjects with AST or ALT values above the normal range remained low in all treatment groups, and there was no trend of increasing proportion of subjects with AST or ALT values above the normal range with time.

### **8.5.2. Kidney function**

#### **8.5.2.1. Pivotal studies**

Overall, shifts from baseline to a worse category in serum creatinine, creatinine clearance and UPCR were infrequent across all treatment groups.

The majority of subjects in each treatment group had serum creatinine values less than or equal to ULN at baseline and remained less than or equal to ULN throughout the study duration (100.0%, 90.9% and 96.4% in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day, and pooled placebo groups, respectively). Overall, there were 11 subjects with serum creatinine greater than 33% increase from baseline at 2 or more consecutive visits (1 [1.8%], 9 [16.4%] and 1 [1.8%] subjects in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day, and pooled placebo groups, respectively). For the majority of subjects in each treatment group, the worst category of post baseline creatinine clearance was greater than or equal to 60mL/min (98.2%, 96.4% and 98.2% in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day, and pooled placebo groups, respectively). The majority of subjects in each treatment group had UPCR less than or equal to 1mg/mg at baseline and remained at less than or equal to 1mg/mg throughout the study duration (96.4%, 94.5% and 100.0% in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day, and pooled placebo groups, respectively).

Three subjects, all in the deferasirox 10 mg/kg/day group, had serum creatinine values that met the notably abnormal criteria of greater than 33% increase from baseline and greater than ULN at 2 consecutive post baseline values. One of these subjects also had creatinine clearance less than 60 mL/min at 2 consecutive post baseline values (pre defined notably abnormal criterion). In addition, 1 patient in the deferasirox 5 mg/kg/day group had creatinine clearance less than 60 mL/min at 2 consecutive post baseline values. Another patient (in the deferasirox 5 mg/kg/day group) had UPCR that met the notably abnormal criterion of greater than or equal to 1.0 mg/mg at 2 consecutive post baseline values.

Over time from baseline to Month 12, mean serum creatinine increased from 48.9 µmol/L at baseline to 53.8 µmol/L at Month 12 (mean change from baseline of 5.0 µmol/L) in the deferasirox 10 mg/kg/day group. Change from baseline in mean serum creatinine at Month 12 was minimal in the deferasirox 5 mg/kg/day group (1.5 µmol/L) and the pooled placebo group (1.9 µmol/L). Mean creatinine clearance decreased from 155.8 mL/min at baseline to 147.5 mL/min at Month 12 (mean change from baseline of -10.1 mL/min) in the deferasirox 10 mg/kg/day group. Change from baseline in mean creatine clearance at Month 12 was smaller in the deferasirox 5 mg/kg/day group (-5.8 mL/min) and the pooled placebo group (-5.3 mL/min). Mean UPCR increased from 0.261 mg/mg at baseline to 0.311 mg/mg at Month 12 (mean change from baseline of 0.031 mg/mg) in the deferasirox 10 mg/kg/day group. Increase from baseline in mean UPCR at Month 12 was smaller in the deferasirox 5 mg/kg/day group (0.015 mg/mg). In the pooled placebo group, there was a small decrease from baseline in mean UPCR at Month 12 (-0.013 mg/mg).

### **8.5.2.2. Other studies**

#### **8.5.2.2.1. Study A2202 core study**

Overall, 11 subjects (22.4% [11 out of 49]; 5 in the deferasirox 10 mg/kg/day group [33.3%; 5 out of 12] and 6 in the deferasirox 15 mg/kg/day group [26.1%; 6 out of 23]) had serum creatinine values that met the notably abnormal criteria of greater than 33% increase from baseline and greater than ULN at 2 consecutive post baseline values. Over time from baseline to Week 24, serum creatinine levels increased with treatment in all dose groups, with greater increases seen in the deferasirox 10 and 15 mg/kg/day groups, compared to in the deferasirox 5 mg/kg/day group. In all dose groups, serum creatinine levels increased from baseline by Week 4, and then remained stable over time to Week 24. Changes from baseline in mean serum creatinine at Week 4 were 8.3 µmol/L, 14.7 µmol/L and 15.5 µmol/L in the deferasirox 5, 10 and 15 mg/kg/day groups, respectively. Changes from baseline in mean serum creatinine at Week 24 were 6.2 µmol/L, 16.9 µmol/L and 13.5 µmol/L, respectively.

The majority of subjects in each dose group had a decrease in creatinine clearance during the core study (63.7%, 80.1% and 82.6% in the deferasirox 5, 10 and 15 mg/kg/day groups, respectively). The majority of the decreases were up to 20% decrease from baseline. Decreases

of greater than 20% from baseline were seen for 2 subjects (18.2%), 4 subjects (26.7%), and 6 subjects (26.1%) in the deferasirox 5, 10 and 15 mg/kg/day groups, respectively.

#### **8.5.2.2.2. Study A2202 core plus extension study**

Overall, 7 subjects (26.9% [7 out of 26]; 2 in the deferasirox 10 mg/kg/day group [33.3%; 2 out of 6] and 5 in the deferasirox 15 mg/kg/day group [45.5%; 5 out of 11]) had serum creatinine values that met the notably abnormal criteria of greater than 33% increase from baseline and greater than ULN at 2 consecutive post baseline values. Over time from baseline to Week 48, serum creatinine levels increased with treatment in all dose groups. Changes from baseline in mean serum creatinine at Week 48 were 12.0 µmol/L, 12.8 µmol/L and 14.8 µmol/L in the deferasirox 5, 10 and 15 mg/kg/day groups, respectively. Over time from baseline to Week 48, the proportion of subjects with serum creatinine values above the normal range remained low in all treatment groups, and there was no trend of increasing proportion of subjects with serum creatinine values above the normal range with time.

The majority of subjects in each dose group had a decrease in creatinine clearance during the core study (88.8%, 83.4% and 100.0 in the deferasirox 5, 10 and 15 mg/kg/day groups, respectively). The majority of the decreases were up to 20% decrease from baseline. Decreases of greater than 20% from baseline were seen for 2 subjects (22.2%), 2 subjects (33.4%), and 4 subjects (36.4%) in the deferasirox 5, 10 and 15 mg/kg/day groups, respectively.

### **8.5.3. Other clinical chemistry**

#### **8.5.3.1. Pivotal study**

Analyses of other clinical chemistry parameters did not show any particular trend with time or with dose compared to placebo, and did not raise any safety concerns.

#### **8.5.3.2. Other studies**

##### **8.5.3.2.1. Study A2202 core study**

Analyses of other clinical chemistry parameters did not show any particular trend with time or with dose, and did not raise any safety concerns.

##### **8.5.3.2.2. Study A2202 core plus extension study**

Analyses of other clinical chemistry parameters did not show any particular trend with time or with dose, and did not raise any safety concerns.

### **8.5.4. Haematology**

#### **8.5.4.1. Pivotal studies**

The majority of subjects in each treatment group had platelet counts greater than or equal to  $100 \times 10^9/L$  at baseline and remained greater than or equal to  $100 \times 10^9/L$  throughout the study duration (98.1%, 94.5% and 89.3% in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day, and pooled placebo groups, respectively). The proportion of subjects with a shift in platelet counts from greater than or equal to  $100 \times 10^9/L$  at baseline to any post baseline value of less than  $100 \times 10^9/L$  was small and generally comparable across treatment groups (1.9% [1 out of 55], 5.5% [3 out of 55] and 7.5% [4 out of 56] in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day, and pooled placebo groups, respectively).

Overall, three subjects each in the 2 deferasirox groups had notably abnormal platelet counts (defined as platelet count less than  $100 \times 10^9/L$ ), compared to 6 in the pooled placebo group. Box plots of platelet counts over time did not show any particular trend with time or with dose compared to placebo.

The majority of subjects in each treatment group had absolute neutrophil counts (ANC) of greater than or equal to  $1.5 \times 10^9/L$  at baseline and remained greater than or equal to  $1.5 \times 10^9/L$  throughout the study duration (91.1%, 95.7% and 93.8% in the deferasirox 5



mg/kg/day, deferasirox 10 mg/kg/day, and pooled placebo groups, respectively). The proportion of subjects with a shift in ANC from greater than or equal to  $1.5 \times 10^9/L$  at baseline to any post baseline value of less than  $1.5 \times 10^9/L$  was low and comparable across treatment groups (4.4% [2 out of 45], 4.3% [2 out of 46] and 6.3% [3 out of 48] in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day, and pooled placebo groups, respectively).

Overall, 3 subjects in the deferasirox 5 mg/kg/day group and 2 subjects in the deferasirox 10 mg/kg/day group had notably abnormal ANC (defined as ANC less than  $1.5 \times 10^9/L$ ), compared to 3 subjects in the pooled placebo group. Box plots of ANC over time did not show any particular trend with time or with dose compared to placebo.

Analyses of other haematology parameters did not show any particular trend with time or with dose compared to placebo, and did not raise any safety concerns.

#### **8.5.4.2. Other studies**

##### **8.5.4.2.1. Study A2202 core study**

The majority of subjects in each treatment group had platelet counts in the normal range at baseline and remained greater than or equal to lower limit of normal (LLN) throughout the study duration (72.7%, 93.3% and 87.7% in the deferasirox 5, 10 and 15 mg/kg/day groups, respectively). There were no shifts to notable values for platelets (less than  $100 \times 10^9/L$ ) in any subjects in the core study. Analysis of platelet counts over time did not show any particular trend with time.

The majority of subjects in each treatment group had ANC in the normal range at baseline and remained greater than or equal to LLN throughout the study duration (72.7%, 66.7% and 69.6% in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day, and deferasirox 15 mg/kg/day groups, respectively). Overall, 1 subject in the deferasirox 5 mg/kg/day group (9.1%; 1/11) and 2 subjects in the deferasirox 15 mg/kg/day group (8.7%; 2/23) had notably abnormal ANC (defined as ANC less than  $1.5 \times 10^9/L$ ). All 3 subjects had ANC in the normal range at baseline. Analysis of ANC over time did not show any particular trend with time.

Analyses of other haematology parameters did not show any particular trend with time or with dose, and did not raise any safety concerns.

##### **8.5.4.2.2. Study A2202 core plus extension study**

The majority of subjects in each treatment group had platelet counts in the normal range at baseline and remained greater than or equal to LLN throughout the study duration (66.7%, 100.0% and 81.8% in the deferasirox 5, 10 and 15 mg/kg/day groups, respectively). There were no shifts to notable values for platelets (less than  $100 \times 10^9/L$ ) in any subjects in the core plus extension study. Analysis of platelet counts over time did not show any particular trend with time.

The majority of subjects in each treatment group had ANC in the normal range at baseline and remained greater than or equal to LLN throughout the study duration (66.7%, 66.7% and 54.5% in the deferasirox 5, 10 and 15 mg/kg/day groups, respectively). Overall, 1 subject in the deferasirox 5 mg/kg/day group (11.1%; 1 out of 9), 1 subject in the deferasirox 10 mg/kg/day group (16.7%; 1 out of 6) and 2 subjects in the deferasirox 15 mg/kg/day group (18.2%; 2 out of 11) had shift in ANC from normal at baseline to any post baseline notably abnormal ANC value (defined as ANC less than  $1.5 \times 10^9/L$ ).

Analyses of other haematology parameters did not show any particular trend with time or with dose, and did not raise any safety concerns.

## 8.5.5. Adverse events of interest

### 8.5.5.1. Pivotal study

Nine groups of AEs of special interest had been pre defined: increased serum creatinine; renal tubular disorders; acute renal failure; increased liver transaminases; hepatic failure; hearing loss; lens opacities, retinal changes and optic neuritis; GI haemorrhage and ulcers, esophagitis; peripheral blood cytopenias. Analyses showed that the incidence of each of these AEs of special interest was low in all treatment groups, with a maximum incidence of 3.6% (that is 2 subjects). There were no subjects in the deferasirox groups with AEs related to hearing loss. There were no subjects in any treatment groups with AEs related to renal tubular disorders or peripheral blood cytopenias.

Analyses of AEs related to renal function showed that AEs of increased serum creatinine were reported for 2 subjects in the study, both in the deferasirox 10 mg/kg/day group. One of these subjects had a mild increase in serum creatinine at Day 301 (117 µmol/L; baseline value: 82 µmol/L), which remained at 117 µmol/L at Day 313. This AE was considered treatment related. Creatinine clearance at Day 301 was 55 mL/min (baseline: 83 mL/min). Study drug was interrupted from Day 314 for one week, and the AE resolved within 3 weeks. The other subject had moderate increase in serum creatinine at Day 258 (127 µmol/L; baseline value: 88 µmol/L), and a creatinine clearance of 68 mL/min (baseline: 98 mL/min). This AE was not considered treatment related although study medication was interrupted from Day 303 to Day 323. The AE resolved within 3 months.

AEs of proteinuria were reported for 2 subjects in the study, both in the deferasirox 5 mg/kg/day group. One of these subjects had mild proteinuria at Day 57 (2319 mg/L; baseline value: 699 mg/L). This AE was not considered treatment related and no action was taken with the study medication. The AE resolved after a week without intervention. The other subject had moderate proteinuria at Day 204 (334 mg/L; baseline value: 191 mg/L). This AE was considered treatment related and led to discontinuation of study drug. The proteinuria was ongoing as of last report.

Analyses of AEs related to hepatic function showed that there were 1 subject with hepatotoxicity (in the deferasirox 5 mg/kg/day group), and 2 with increased ALT or AST (1 subject each in the 2 deferasirox groups). In the patient with AE of hepatotoxicity, the event onset occurred after 1 year of treatment. The subject presented with concurrent jaundice and right upper quadrant pain. The actual daily dose was 5.7 mg/kg/day at the time of event onset. The event was an SAE and considered to be treatment related. The subject was hospitalised and study medication was temporarily interrupted. No clinical laboratory values were available for the SAE as the patient was hospitalised outside the investigational site. The patient completed the core study with the event ongoing. One subject in the deferasirox 10 mg/kg/day group had elevated ALT and AST at baseline (ALT: 106 U/L; AST: 64 U/L), and had a further increase in ALT in the second week of treatment (Day 19: 185 U/L), associated with an increase in AST (Day 19: 457 U/L). The event was considered treatment related. No action was taken with the study medication and the event resolved after one week without intervention. One subject in the deferasirox 5 mg/kg/day group was dose escalated to 10 mg/kg/day at Visit 12 (Day 175) based on LIC results as per protocol and had a mildly increased AST at Day 232 (42 U/L; baseline: 21 U/L). The actual deferasirox dose at the time of the event was 10.7 mg/kg/day. This AE was not considered treatment related and no action was taken with the study medication. The event was resolved without intervention by Day 260.

Analyses of AEs related to GI haemorrhage and ulcers or esophagitis showed that 1 subject had melena reported as an AE (in the deferasirox 10 mg/kg/day group). The severity of the event was reported as mild. The AE was considered treatment related. Study drug was temporarily interrupted due to this event, and was not restarted as the subject developed SAEs of antral

gastritis and acute duodenal ulcer due to *Helicobacter pylori* infection. The AE resolved after 2 days.

In Study A2209, GI events were also analysed using the following preferred terms: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, dyspepsia, gastrointestinal pain, diarrhoea, loose stools, frequent bowel movements, nausea, vomiting. Results showed that the proportion of subjects with at least one GI AE was lower in the deferasirox 5 mg/kg/day group (16.4%; 9 out of 55) compared to the deferasirox 10 mg/kg/day group (32.7%, 18 out of 55) and the pooled placebo group (30.4%, 17 out of 56). The number of subjects who had GI events that led to interruption of study drug within 10 days of event onset was small across all treatment groups: 1 subject in the deferasirox 5 mg/kg/day group, 2 subjects in the deferasirox 10 mg/kg/day group, and 1 subject in each of the placebo groups. All GI events requiring dose interruption resolved during the study. The median duration of all GI events was 5.0, 6.5 and 2.5 days in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day and pooled placebo groups, respectively, and ranged from 1 to 8 days across all groups.

AEs related to lens opacities, retinal changes and optic neuritis were reported in 2 subjects, 1 in the deferasirox 5 mg/kg/day group (AE of cataract), and the other in the placebo 10 mg/kg/day group (AE of optic neuritis). Neither AE was considered treatment related. The subject in the deferasirox 5 mg/kg/day group had pre existing cataract and was hospitalised and underwent surgery for cataract. The subject in the placebo 10 mg/kg/day group was hospitalised with a diagnosis of optic neuritis due to compression of the right optic nerve. In addition, a third subject (in deferasirox 5 mg/kg/day group) had early cataract noted on ophthalmologic examination at screening, which had worsened to advanced cataract of the left eye at the end of study visit ophthalmologic examination. No ocular AE was reported for this subject.

Auditory examinations at screening and at the end of study visit detected right, mild sensory neural hearing loss at the end of study visit in 1 subject in the placebo 10 mg/kg/day group. The event was reported as an AE. None of the subjects in the deferasirox groups had new or worsened abnormal findings on auditory examinations.

In Study A2209, skin rash events were also analysed using the following preferred terms: drug eruption, rash, rash erythematous, rash generalised, rash macular, rash maculo papular, rash papular, rash pruritic, rash morbilliform, rash vesicular, rash maculovesicular. Only rash persistent for more than 1 week or severe rash was considered. Results showed that the proportion of subjects with at least one such AE was low across all treatment groups (1.8% [1 out of 55], 5.5% [3 out of 55] and 1.8% [1 out of 56] in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day and pooled placebo groups, respectively). One of the subjects in the deferasirox 10 mg/kg/day group had 2 episodes of severe or persistent rash, while the other subjects had a single episode each. Study drug was interrupted within 10 days of event onset for 2 of the subjects in the deferasirox 10 mg/kg/day group.

### **8.5.5.2. Other studies**

#### **8.5.5.2.1. Study A2202 core study**

The nine groups of AEs of special interest were the same as those in Study A2209. Analyses showed that the incidences of these AEs of special interest appeared to be higher in the deferasirox 10 and 15 mg/kg/day groups, compared to in the deferasirox 5 mg/kg/day group. There were no subjects in any treatment groups with AEs related to renal tubular disorders, hepatic failure or peripheral blood cytopenias. The most frequent AEs of special interest were increased serum creatinine (0.0%, 20.0% and 26.1% in the deferasirox 5, 10 and 15 mg/kg/day groups, respectively) and increased liver transaminases (0.0%, 20.0% and 21.7%, respectively). None of these AEs were reported as SAEs.

In Study A2202, incidences of moderate or severe skin rash events were analysed. Results showed that the proportion of subjects with at least one such AE was low and occurred only in the deferasirox 15 mg/kg/day group. In the core study, moderate skin rash was reported for 2

subjects (8.7%; 2 out of 23), and severe skin rash was reported for 1 subject (4.3%; 4 out of 23). No additional events were reported in the extension phase.

#### **8.5.5.2.2. Study A2202 core plus extension study**

Analyses of the AEs of special interest in the extension safety population also showed that the incidences of these AEs appeared to be higher in the deferasirox 10 and 15 mg/kg/day groups, compared to in the deferasirox 5 mg/kg/day group. There were no subjects in any treatment groups with AEs related to renal tubular disorders, hepatic failure, GI haemorrhage and ulcers or esophagitis, or peripheral blood cytopenias. The most frequent AEs of special interest were increased serum creatinine (11.1%, 33.3% and 27.3% in the deferasirox 5, 10 and 15 mg/kg/day groups, respectively). None of these AEs were reported as SAEs.

### **8.5.6. Electrocardiograph and echocardiography**

#### **8.5.6.1. Pivotal study**

Overall, 3 subjects (2 in the deferasirox 10 mg/kg/day group and 1 in the deferasirox 5 mg/kg/day group) had new or worsened clinically significant abnormality on ECG examination. One subject in the deferasirox 5 mg/kg/day group had left ventricular hypertrophy detected on ECG examination at the end of study visit. The event was reported as an AE and was not considered to be treatment related. One subject in the deferasirox 10 mg/kg/day group had non-specific intraventricular conduction delay detected on ECG examination at the end of study visit. The event was reported as an AE and was not considered to be treatment related. Another subject in the deferasirox 10 mg/kg/day group had atrial fibrillation reported at an unscheduled visit on Day 378 and again at end of study visit on Day 392. The event was reported as an SAE and was not considered to be treatment related.

Echocardiography was performed at screening and at end of study visit. The results were not presented in the CSR. It is unclear to the evaluator if this is to be taken to mean that there were no new or worsened clinically significant abnormalities found in the echocardiography tests. This will be raised as a clinical question.

#### **8.5.6.2. Other studies**

##### **8.5.6.2.1. Study A2202 core study**

Overall 1 subject (in the deferasirox 10 mg/kg/day group) had a new or worsened clinically significant abnormality on ECG examination (T wave abnormality). No additional abnormalities were noted in the extension study.

### **8.5.7. Vital signs**

#### **8.5.7.1. Pivotal study**

Analyses of vital signs did not raise any safety concerns.

#### **8.5.7.2. Other studies**

##### **8.5.7.2.1. Study A2202 core study**

Analyses of vital signs in the core and extension studies did not raise any safety concerns.

## **8.6. Safety issues with the potential for major regulatory impact**

### **8.6.1. Liver toxicity**

In Study A2209, the overall incidence of AEs related to hepatic function was low (n=3). One subject in the deferasirox 5 mg/kg/day group had a treatment related SAE of hepatotoxicity. Another subject in the deferasirox 10 mg/kg/day group had a treatment related AE of an increase in ALT, and a third subject in the deferasirox 5 mg/kg/day group had a non treatment related AE of an increase in AST. These have been discussed earlier.

In Study A2209, the majority of subjects in each treatment group (deferasirox 5 mg/kg/day group, deferasirox 10 mg/kg/day group and pooled placebo group) had ALT and AST values within normal range at baseline and remained within the normal range throughout the study duration (ALT: 60% to 70%; AST: 60% to 76%). The proportion of subjects with a shift to a maximum post baseline AST of greater than 2.5 times ULN (that is Grade 2 and above) from a baseline AST of lower grades was low and comparable among treatment groups (4% to 7%), while that for ALT was also low across all treatment groups, but higher in the deferasirox 10 mg/kg/day group (10.9%) compared to the deferasirox 5 mg/kg/day (7.3%) and the pooled placebo group (5.4%). The incidence of notably abnormal transaminases was low (n=2), involving 1 subject each in the deferasirox 10 mg/kg/day group and the 10 mg/kg/day placebo group. Over time from baseline to Month 12, mean ALT and AST values decreased in both deferasirox groups. These have been discussed earlier.

Results in Study A2202 were generally consistent with those seen in Study A2209. These have been discussed earlier, but will be summarised here for ease of reference. No subjects in any treatment groups had AE of hepatic failure in the core as well as extension studies. The incidences of increased liver transaminases reported as AEs were low in both the core and extension studies, but were higher in the deferasirox 10 and 15 mg/kg/day groups (20.0% and 21.7%, respectively) compared to the 5 mg/kg/day group (0.0%) in the core study. None of these AEs were reported as SAEs. The proportions of subjects with a shift to any post baseline AST or ALT of greater than ULN from a normal baseline AST or ALT were low across the treatment groups, but higher in the deferasirox 10 and 15 mg/kg/day groups compared to the 5 mg/kg/day group in the core study. In the core plus extension study (that is in the extension safety population), the proportion of such subjects with reference to ALT were comparable across the 3 dose groups, while that with reference to AST was higher in the 15 mg/kg/day group compared to the 5 and 10 mg/kg/day groups. There were no subjects with post baseline ALT or AST greater than 10 times ULN, or AST greater than 5 times ULN in the core as well as extension studies. Three subjects who had ALT greater than 5 times ULN in the core study were all in the 15 mg/kg/day group, and there were no additional subjects with ALT greater than 5 times ULN with onset during the extension study. Over time from baseline to Week 48, the proportion of subjects with AST or ALT values above the normal range remained low in all treatment groups, and there was no trend of increasing proportion of subjects with AST or ALT values above the normal range with time.

### **8.6.2. Renal toxicity**

In Study A2209, the overall incidence of AEs related to renal function was low (n=4). There were no subjects in any treatment groups with AEs of renal tubular disorders. Two subjects in the deferasirox 10 mg/kg/day group had AEs of increased serum creatinine, one of which was considered treatment related, while the other was not. Two subjects in the deferasirox 5 mg/kg/day group had AEs of proteinuria, one of which was considered treatment related, while the other was not. These have been discussed earlier.

In Study A2209, the majority of subjects in each treatment group had serum creatinine values less than or equal to ULN at baseline and remained less than or equal to ULN throughout the study duration (91% to 100%). In addition, for the majority of subjects in each treatment group, the worst category of post baseline creatinine clearance was greater than or equal to 60mL/min (96% to 98%). The majority of subjects in each treatment group also had UPCr less than or equal to 1mg/mg at baseline and remained less than or equal to 1mg/mg throughout the study duration (95% to 100%). The incidence of notably abnormal serum creatinine (n=3), creatinine clearance (n=2) or UPCr (n=1) was low. Over time from baseline to Month 12, mean serum creatinine increased and mean creatinine clearance decreased in the deferasirox 10 mg/kg/day group (mean change from baseline of 5.0 µmol/L and -10.1 mL/min, respectively). Changes from baseline in mean serum creatinine and mean creatinine clearance were comparable between the deferasirox 5 mg/kg/day group and the pooled placebo group, and were smaller

compared to those in the deferasirox 10 mg/kg/day group. There was also a greater increase from baseline to Month 12 in mean UPCr in the deferasirox 10 mg/kg/day group (change from baseline of 0.031 mg/mg) compared to the deferasirox 5 mg/kg/day group (0.015 mg/mg) and the pooled placebo group (-0.013 mg/mg). These have been discussed earlier.

Results in Study A2202 were consistent with those seen in Study A2209. These have been discussed earlier, but will be summarised here for ease of reference. No subjects in any treatment groups had AEs of renal tubular disorders in the core as well as extension studies. The incidences of increased serum creatinine reported as AEs were low in both the core and extension studies, but were higher in the deferasirox 10 and 15 mg/kg/day groups (core study: 20.0% and 26.1%, respectively; extension plus core study: 33.3% and 27.3%, respectively) compared to the 5 mg/kg/day group (core study: 0.0%; extension plus core study: 11.1%). None of these AEs were reported as SAEs. The incidence of notably abnormal serum creatinine values were higher in the deferasirox 10 and 15 mg/kg/day groups compared to the 5 mg/kg/day group in both the core study (26% to 33% in the 10 and 15 mg/kg/day groups versus 0% in the 5 mg/kg/day group) and the core plus extension study (33% to 46% versus 0%). In the core study, serum creatinine levels increased with time in all dose groups, with greater increases seen in the deferasirox 10 and 15 mg/kg/day groups, compared to in the deferasirox 5 mg/kg/day group. In all dose groups, serum creatinine levels increased from baseline by Week 4, and then remained stable over time to Week 24. At Week 24, changes from baseline in mean serum creatinine were 6.2  $\mu\text{mol/L}$ , 16.9  $\mu\text{mol/L}$  and 13.5  $\mu\text{mol/L}$  in the deferasirox 5, 10 and 15 mg/kg/day groups, respectively. In the extension safety population, changes from baseline in mean serum creatinine at Week 48 were 12.0  $\mu\text{mol/L}$ , 12.8  $\mu\text{mol/L}$  and 14.8  $\mu\text{mol/L}$ , respectively. Over time from baseline to Week 48, the proportion of subjects with serum creatinine values above the normal range remained low in all treatment groups, and there was no trend of increasing proportion of subjects with serum creatinine values above the normal range with time. In both the core study and the core plus extension study, the majority of subjects in each dose group had a decrease in creatinine clearance during the core study but the majority of the decreases were up to 20% decrease from baseline. Decreases of greater than 20% from baseline were generally comparable across the dose groups.

### 8.6.3. Haematological toxicity

In Study A2209, the majority of subjects in each treatment group had platelet counts greater than or equal to  $100 \times 10^9/\text{L}$  at baseline and remained greater than or equal to  $100 \times 10^9/\text{L}$  throughout the study duration (89% to 98%). The proportion of subjects with a shift in platelet counts from greater than or equal to  $100 \times 10^9/\text{L}$  at baseline to any post baseline value of less than  $100 \times 10^9/\text{L}$  was comparable across treatment groups. The proportion of subjects with notably abnormal platelet counts (defined as platelet count less than  $100 \times 10^9/\text{L}$ ) was lower in the deferasirox 5 mg/kg/day group (5.5%) and the deferasirox 10 mg/kg/day group (5.5%), compared to the pooled placebo group (10.7%). These have been discussed earlier.

The majority of subjects in each treatment group also had ANC of greater than or equal to  $1.5 \times 10^9/\text{L}$  at baseline and remained greater than or equal to  $1.5 \times 10^9/\text{L}$  throughout the study duration (91% to 96%). The proportion of subjects with a shift in ANC from greater than or equal to  $1.5 \times 10^9/\text{L}$  at baseline to any post baseline value of less than  $1.5 \times 10^9/\text{L}$  was comparable across treatment groups. The proportion of subjects with notably abnormal ANC (defined as ANC less than  $1.5 \times 10^9/\text{L}$ ) was low and comparable across treatment groups. These have been discussed earlier.

Results in Study A2202 were consistent with those seen in Study A2209. These have been discussed earlier, but will be summarised here for ease of reference. There were no shifts to notable values for platelets (less than  $100 \times 10^9/\text{L}$ ) in any subjects in the core as well as the extension studies. Analysis of platelet counts over time did not show any particular trend with time. The proportion of subjects with shifts in ANC from normal at baseline to any post baseline notably abnormal ANC value (defined as ANC less than  $1.5 \times 10^9/\text{L}$ ) was low in both the core

study and the core plus extension study, with a maximum number of 2 such subjects in any treatment group.

#### **8.6.4. Skin reactions**

In Study A2209, the overall incidence of rash persistent for more than 1 week or severe rash was low (1.8%, 5.5% and 1.8% in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day and pooled placebo groups, respectively). These have been discussed earlier. Results in Study A2202 were consistent with those seen in Study A2209 showing that the proportion of subjects with at least one moderate or severe skin rash AE was low and occurred only in the deferasirox 15 mg/kg/day group (n=2 for moderate skin rash; n=1 for severe skin rash) in the core study. No additional moderate or severe skin rash AEs were reported in the extension phase.

#### **8.6.5. Gastrointestinal haemorrhage**

In Study A2209, analyses of AEs related to GI haemorrhage and ulcers or esophagitis showed that only 1 subject in the study had such AEs (melena; in the deferasirox 10 mg/kg/day group). The severity of the event was reported as mild, and was resolved after 2 days. These have been discussed earlier. Results in Study A2202 were consistent with those seen in Study A2209, with a low incidence of these AEs (1 subject [in deferasirox 15 mg/kg/day group] reporting gastrointestinal pain as an AE in the core study; none in the core plus extension study).

### **8.7. Other safety issues**

#### **8.7.1. Safety in special populations**

In Study A2209, AEs and laboratory results were analysed by demographic subgroups (gender, race, age), by baseline LIC (less than or equal to 7, greater than 7 to 15, and greater than 15 mg Fe/g dw) and serum ferritin (greater than 300 to 500, greater than 500 to 1000, and greater than 1000 µg/L) categories, and by underlying disease subgroups (beta thalassaemia, alpha thalassaemia, HbE beta thalassaemia). Results did not raise particular safety concerns for any specific subgroup.

In particular, no subjects less than 18 years of age in the study had notably abnormal serum creatinine (serum creatinine greater than 33% increase from baseline and greater than ULN at greater than or equal to 2 consecutive post baseline values), creatinine clearance (creatinine clearance less than 60 mL/min at greater than or equal to 2 consecutive post baseline values), UPCR (UPCR greater than or equal to 1.0 mg/mg at greater than or equal to 2 consecutive post baseline values), ALT (ALT values of greater than 5 times ULN and greater than 2 times baseline), AST (AST values of greater than 5 times ULN and greater than 2 times baseline) or absolute neutrophil count (less than  $1.5 \times 10^9/L$ ). Analyses of the incidence of AEs, severe AEs, treatment related AEs and AEs leading to permanent study drug discontinuation in the subgroups of subjects aged less than 18 and greater than or equal to 18 years did not raise any safety concerns, although the small sample size in the subgroup of subjects aged less than 18 years makes interpretation difficult.

No subgroup analyses were performed for Study A2202.

### **8.8. Post marketing experience**

The sponsor had stated that safety data from all sources (literature, studies, spontaneous reporting) were reviewed on an ongoing basis, and had provided a summary of the conclusions of the most recent periodic safety update report covering the time period from 1 May 2010 to 31 October 2010. During this reporting period, there were no regulatory or manufacturer actions taken for safety reasons. No new major safety findings had been identified.

## 8.9. Evaluator's overall conclusions on clinical safety

Overall, the safety results of the pivotal study (A2209) were consistent with the known safety profile and adverse effects of deferasirox. In Study A2209, the incidences of all causality AEs, SAEs, and AEs leading to discontinuation of study drug were comparable between the 2 deferasirox groups and the pooled placebo group. The incidence of treatment related AEs was higher in the deferasirox 5 and 10 mg/kg/day groups (23.6% and 32.7%, respectively) compared to the pooled placebo group (16.1%).

The AEs elicited in this pivotal study are known adverse effects of deferasirox described in the currently approved Australian PI for deferasirox, in which it is stated that the most frequent adverse reactions reported in adult and paediatric patients with transfusional iron overload treated with deferasirox were gastrointestinal disturbances (mainly nausea, vomiting, diarrhoea, or abdominal pain) and skin rash. These reactions had been found to be dose dependent, mostly mild to moderate, generally transient and mostly resolved even if treatment was continued. Mild, non progressive increases in serum creatinine, mostly within the normal range, occurred in about 36% of these patients, and these were dose dependent, often resolved spontaneously and could sometimes be alleviated by reducing the dose. Elevations of liver transaminases were reported in about 2% of these patients. These were not clearly dose related and elevations of transaminases greater than 10 times the upper limit of the normal range were uncommon (0.3%). Adverse drug reactions listed as common in the currently approved Australian PI are headache, gastrointestinal disorders (diarrhoea, constipation, vomiting, nausea, abdominal pain, abdominal distension, dyspepsia), transaminases increased, rash, pruritus, proteinuria, and blood creatinine increased (very common).

The profile of treatment-related AEs in study A2209 was consistent with the above safety profile. The most commonly reported treatment related AEs in the deferasirox 5 and 10 mg/kg/day groups in Study A2209 were nausea (5.5%, 7.3% and 7.1% in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day, and pooled placebo groups, respectively), diarrhoea (0.0%, 9.1% and 1.8%, respectively) and rash (3.6%, 9.1% and 1.8%, respectively). The incidence of treatment related SAEs was low (n=4; 3 in the deferasirox 5 mg/kg/day group, and 1 in the deferasirox 10 mg/kg/day group) and the SAEs involved were also consistent with the known adverse effects of deferasirox (treatment related SAEs of abdominal pain, cellulitis and liver toxicity in the deferasirox 5 mg/kg/day group, and of pruritus and rash in the deferasirox 10 mg/kg/day group). There were no deaths during the study.

Analyses of effect on renal function showed dose dependent increases in serum creatinine over time, which is consistent with the known adverse effects of deferasirox as reported in the currently approved PI. Over time from baseline to Month 12, mean serum creatinine increased and mean creatinine clearance decreased in the deferasirox 10 mg/kg/day group (mean change from baseline of 5.0  $\mu\text{mol/L}$  and -10.1 mL/min, respectively), while changes from baseline in mean serum creatinine and mean creatinine clearance were comparable between the deferasirox 5 mg/kg/day group and the pooled placebo group, and were smaller compared to those in the deferasirox 10 mg/kg/day group. The incidences of notably abnormal serum creatinine (n=3; all in the deferasirox 10 mg/kg/day group), creatinine clearance (n=2; 1 each in the deferasirox 5 and 10 mg/kg/day groups) or UPCR (n=1; in the deferasirox 5 mg/kg/day group) were low. In addition, for the majority of subjects in each treatment group (96 to 98%), the worst category of post baseline creatinine clearance was greater than or equal to 60mL/min. The overall incidence of AEs related to renal function was also low (n=4), out of which only 2 were considered treatment related (1 event of increased serum creatinine in the deferasirox 10 mg/kg/day group, and 1 event of proteinuria in the deferasirox 5 mg/kg/day group).

Analyses of effect on transaminases also showed results consistent with the known adverse effects of deferasirox as reported in the currently approved PI. The proportion of subjects with a shift to a maximum post baseline AST of greater than 2.5 times ULN from a baseline AST of



lower grades was low and comparable among treatment groups (4% to 7%), while that for ALT was also low across all treatment groups, but higher in the deferasirox 10 mg/kg/day group (10.9%) compared to the deferasirox 5 mg/kg/day (7.3%) and the pooled placebo group (5.4%). The incidence of notably abnormal transaminases was low (n=2), involving 1 subject each in the deferasirox 10 mg/kg/day group and the 10 mg/kg/day placebo group. There was no trend of increasing ALT or AST with time (mean ALT and AST values decreased over time from baseline to Month 12 in both deferasirox groups). The overall incidence of AEs related to hepatic function was also low (n=3), out of which 2 were considered treatment related (1 treatment related SAE of hepatotoxicity in the deferasirox 5 mg/kg/day group, and 1 treatment related AE of an increase in ALT in the deferasirox 10 mg/kg/day group).

The currently approved PI for deferasirox states that there have been post marketing reports (both spontaneous and from clinical trials) of cytopenias, although most of these patients had pre existing haematological disorders that were frequently associated with bone marrow failure. Analyses of effect of deferasirox on platelets and ANC in Study A2209 did not raise any major safety concerns. The proportion of subjects with a shift in platelet counts from greater than or equal to  $100 \times 10^9/L$  at baseline to any post baseline value of less than  $100 \times 10^9/L$ , and the proportion of subjects with a shift in ANC from greater than or equal to  $1.5 \times 10^9/L$  at baseline to any post baseline value of less than  $1.5 \times 10^9/L$  were small and generally comparable across treatment groups. Box plots of platelet counts and ANC over time did not show any particular trend with time or with dose compared to placebo. There were no subjects in the deferasirox groups with AEs related to peripheral blood cytopenias.

While gastrointestinal AEs were common (most commonly reported treatment related AEs in Study A2209 included nausea and diarrhoea), the incidence of AEs related to GI haemorrhage and ulcers or esophagitis was low (n=1, deferasirox 10 mg/kg/day group). While skin rash AEs were common (rash was one of the most commonly reported treatment related AEs in Study A2209), the overall incidence of rash persistent for more than 1 week or severe rash was low (1.8%, 5.5% and 1.8% in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day and pooled placebo groups, respectively).

The currently approved PI for deferasirox states that

*As with other iron chelator treatment, high-frequency hearing loss and lenticular opacities (early cataracts) have been uncommonly observed in patients treated with Exjade.*

In Study A2209, no subjects in the deferasirox groups had AEs related to hearing loss. AEs related to lens opacities, retinal changes and optic neuritis were reported in 1 subject in the deferasirox groups (deferasirox 5 mg/kg/day group; AE of cataract), but was not considered to be treatment related.

Safety results in Study A2202 on the use of deferasirox 5 to 15 mg/kg/day in patients with HH yielded results in keeping with those in Study A2202, and with the known safety profile of deferasirox. No major safety concerns are triggered by the safety results in Study A2202.

The proposed additional indication is targeted towards a patient population aged 10 years and above, and hence includes paediatric NTDT patient population aged 10 to less than 18 years. Safety analyses in the age subgroups less than 18 years and greater than or equal to 18 years in Study A2209 did not raise any major concerns, although the overall small sample size of subjects less than 18 years of age makes interpretation difficult. Analyses of the incidence of AEs, severe AEs, treatment related AEs and AEs leading to permanent study drug discontinuation in the subgroups of subjects aged less than 18 versus greater than or equal to 18 years did not raise any major safety concerns. In particular, no subjects less than 18 years of age in the study had notably abnormal serum creatinine, creatinine clearance, UPCR, ALT, AST or absolute neutrophil count.

Although 2 starting doses of deferasirox were tested in this study, the recommended starting dose in the proposed PI was deferasirox 10 mg/kg/day. Overall, safety results showed that

although the incidences of the most commonly reported treatment related AEs (nausea, diarrhoea and rash) were higher in the deferasirox 10 mg/kg/day group compared to the 5 mg/kg/day group (nausea: 7.3% versus 5.5%; diarrhoea: 9.1% versus 0.0%; rash: 9.1% versus 3.5%) and that there were dose dependent increases in serum creatinine over time, this is consistent with the known safety profile of deferasirox as stated in the currently approved PI, and the safety results for deferasirox 10 mg/kg/day did not raise any major safety concerns. The overall incidences of all causality AEs, SAEs, AEs leading to discontinuation, and treatment related AEs were comparable between the 2 deferasirox groups. The incidence of treatment related SAEs in the deferasirox 10 mg/kg/day group was low (1 subject; versus 3 in the deferasirox 5 mg/kg/day group). Although the incidences of gastrointestinal AEs and skin rash were higher in the 10 compared to the 5 mg/kg/day group, the incidence of AEs related to GI haemorrhage and ulcers or esophagitis in the deferasirox 10 mg/kg/day group was low (1 subject; versus 0 subject in the deferasirox 5 mg/kg/day group), as was the incidence of rash persistent for more than 1 week or severe rash (3 subjects; versus 1 subject in the deferasirox 5 mg/kg/day group), as well as the incidence of notably abnormal serum creatinine (3 subjects; versus 0 subjects in the deferasirox 5 mg/kg/day group), and of notably abnormal creatinine clearance (1 subject; versus 1 subject in the deferasirox 5 mg/kg/day group). For the majority of subjects in the deferasirox 10 mg/kg/day group (96.4%) the worst category of post baseline creatinine clearance was greater than or equal to 60mL/min. The overall incidence of any treatment related AEs related to renal function in the deferasirox 10 mg/kg/day group was also low (1 event of increased serum creatinine). The proportion of subjects with a shift to a maximum post baseline AST or ALT of greater than 2.5 times ULN (that is, Grade 2 and above) from a baseline AST or ALT of lower grades was low in the deferasirox 10 mg/kg/day group (3 subjects [5.5%] and 6 subjects [10.9%] for AST and ALT, respectively). The incidence of notably abnormal transaminases in the deferasirox 10 mg/kg/day group was low (1 subject), as was the incidence of treatment related AEs related to hepatic function (1 event of an increase in ALT). Analyses of haematological parameters did not raise any safety concerns in the deferasirox 10 mg/kg/day group, and there were no incidences of AEs related to hearing loss or to lens opacities, retinal changes and optic neuritis in the deferasirox 10 mg/kg/day group.

## 9. First round benefit-risk assessment

### 9.1. First round assessment of benefits

The benefits of deferasirox in the proposed usage are:

- Treatment of chronic iron overload in patients with NTDT aged 10 years and older, and hence potential reduction of morbidity associated with chronic iron overload in these patients.

In Study A2209, efficacy analyses of the change in LIC from baseline at Week 24 showed no statistically significant difference between either deferasirox dose group (5 and 10 mg/kg/day) and the pooled placebo group. However, by Week 52, there were statistically significantly greater decreases from baseline in LIC compared to the pooled placebo group for both deferasirox 5 mg/kg/day (-1.95 Fe/g dw versus 0.38 Fe/g dw in the pooled placebo group,  $p=0.001$ ) as well as deferasirox 10 mg/kg/day (-3.80 Fe/g dw versus 0.38 Fe/g dw,  $p<0.001$ ). Comparison between deferasirox 5 mg/kg/day and deferasirox 10 mg/kg/day showed that the decrease from baseline in LIC at Week 52 was statistically significantly greater for deferasirox 10 mg/kg/day group compared to deferasirox 5 mg/kg/day ( $p=0.009$ ). Supportive analyses on the PPS, and by using an ANOVA model instead of the ANCOVA model, yielded similar results. Subgroup analyses on the primary efficacy outcome also yielded results consistent with the analysis in the overall population.

## 9.2. First round assessment of risks

The risks of deferasirox in the proposed usage are:

- Increases in serum creatinine
- Increases in transaminases
- Skin rash
- Gastrointestinal disturbances

Overall, the safety results of Study A2209 were consistent with the known adverse effects of deferasirox. Safety analyses with regards to increases in serum creatinine, increases in transaminases, skin rash and gastrointestinal disturbances also yielded results consistent with known effects of deferasirox and did not raise any major safety concerns.

Analyses of effect on renal function showed dose dependent increases in serum creatinine and decreases in creatinine clearance over time, which is consistent with the known effect of deferasirox as reported in the currently approved PI. However, the incidences of notably abnormal serum creatinine, creatinine clearance or UPCR were low. In addition, for the majority of subjects in each treatment group (96 to 98%), the worst category of post baseline creatinine clearance was greater than or equal to 60mL/min. The overall incidence of AEs related to renal function was also low (n=4), out of which only 2 were considered treatment related (1 event of increased serum creatinine in the deferasirox 10 mg/kg/day group, and 1 event of proteinuria in the deferasirox 5 mg/kg/day group).

Analyses of effect on transaminases also showed results consistent with the known effect of deferasirox as reported in the currently approved PI. The proportion of subjects with a shift to a maximum post baseline AST or ALT of greater than 2.5 times ULN from a baseline AST or ALT of lower grades was low and comparable among treatment groups (AST: 4% to 7%; ALT: 5% to 11%). The incidence of notably abnormal transaminases was low (n=2; 1 subject each in the deferasirox 10 mg/kg/day group and the 10 mg/kg/day placebo group), as was the incidence of treatment related AEs related to hepatic function (n=2; 1 treatment related SAE of hepatotoxicity in the deferasirox 5 mg/kg/day group, and 1 treatment related AE of an increase in ALT in the deferasirox 10mg/kg/day group). There was no trend of increasing ALT or AST with time.

The most commonly reported treatment related AEs in the deferasirox 5 and 10 mg/kg/day groups in Study A2209 were related to GI disturbances and rash: nausea (5.5%, 7.3% and 7.1% in the deferasirox 5 mg/kg/day, deferasirox 10 mg/kg/day, and pooled placebo groups, respectively), diarrhoea (0.0%, 9.1% and 1.8%, respectively) and rash (3.6%, 9.1% and 1.8%, respectively), which is consistent with the known adverse effects of deferasirox. The number of subjects who had GI adverse events that led to interruption of study drug within 10 days of event onset was small (1 and 2 subjects in the deferasirox 5 and 10 mg/kg/day groups, respectively), and the duration of these GI events was relatively short (median duration of all GI events was 5.0 and 6.5 days in the deferasirox 5 and 10 mg/kg/day groups, respectively; duration ranged from 1 to 8 days across all treatment groups). The incidence of AEs related to GI haemorrhage and ulcers or esophagitis was low (n=1, deferasirox 10 mg/kg/day group), as was the incidence of rash persistent for more than 1 week or severe rash (1.8% and 5.5% in the deferasirox 5 and 10 mg/kg/day groups, respectively).

## 9.3. First round assessment of benefit-risk balance

The benefit-risk balance of deferasirox, given the proposed usage, is favourable.

Although 2 starting doses of deferasirox were tested in Study A2209, the recommended starting dose in the proposed PI was deferasirox 10 mg/kg/day. Evaluation of the benefit-risk profiles of

the 2 doses of deferasirox tested in Study A2209 showed that the choice of deferasirox 10 mg/kg/day is appropriate. Efficacy analyses showed that there was a statistically significantly greater decrease from baseline in LIC at Week 52 with deferasirox 10 mg/kg/day compared to deferasirox 5 mg/kg/day. Although safety analyses showed that there were higher incidences of the most commonly reported treatment related AEs (nausea, diarrhoea and rash) with deferasirox 10 mg/kg/day compared to the 5 mg/kg/day, as well as greater increases in serum creatinine over time, these dose dependent safety results were consistent with the known safety profile of deferasirox as stated in the currently approved PI. In addition, evaluation of the safety results of deferasirox 10 mg/kg/day did not raise any major safety concerns, despite the relatively higher incidences compared to deferasirox 5 mg/kg/day.

With regards to efficacy results, analyses of the mean change from baseline in LIC at Week 52 by the actual average daily dose of deferasirox administered to the subjects during Study A2209 showed that there was a dose response effect in this efficacy endpoint, where subjects on an actual average daily dose ranges of deferasirox of greater than 0 to less than 7.5 mg/kg/day, greater than or equal to 7.5 to less than or equal to 12.5 mg/kg/day and greater than 12.5 to less than or equal to 17.5 mg/kg/day had mean change from baseline in LIC at Week 52 of -1.72, -3.56 and -4.22 Fe/g dw, respectively. By Week 52, there were statistically significantly greater decreases from baseline in LIC in the deferasirox 10 mg/kg/day compared to the deferasirox 5 mg/kg/day (-3.80 Fe/g dw versus -1.95 Fe/g dw;  $p=0.009$ ). There are no internationally accepted treatment guidelines regarding the recommended or target amount of decrease in LIC in patients with NTDT, but, a literature search showed mention of criteria for initiation of iron chelation therapy in NTDT patients as LIC greater than 3 to 6 mg Fe/g dw. Results in Study A2209 showed that, by Week 52, the proportion of subjects with LIC less than 5 mg Fe/g dw or less than 3 mg Fe/g dw was 27.3% and 9.1%, respectively in the deferasirox 10 mg/kg/day group, compared with only 14.5% and 1.8%, respectively, in the deferasirox 5 mg/kg/day group. By Week 52, the proportion of subjects with an LIC decrease from baseline of at least 3 mg Fe/g dw was 56.4% in the deferasirox 10 mg/kg/day group compared with 32.7% in the deferasirox 5 mg/kg/day group, and the proportion of subjects with an LIC decrease from baseline of at least 30% was 49.1% in the deferasirox 10 mg/kg/day group compared with 25.5% in the deferasirox 5 mg/kg/day group.

In addition, although the proportion of subjects who needed to have dose escalation due to suboptimal response (that is, those with less than 15% decrease in LIC and with LIC greater than or equal to 7 mg Fe/g dw) at Week 24 was comparable between the 5 mg/kg/day (47.3%) and 10 mg/kg/day groups (45.5%), subsequent analyses at Week 52 showed that subjects who remained on 5 mg/kg/day of deferasirox ended up having smaller decrease from baseline in LIC at Week 52 (change from baseline of -1.88 Fe/g dw) compared to previously at Week 24 (change from baseline of -2.61 Fe/g dw). In contrast, subjects who remained on 10 mg/kg/day of deferasirox after Week 24 had sustained effect, showing further decrease from baseline in LIC at Week 52 (change from baseline of -3.57 Fe/g dw) compared to at Week 24 (change from baseline of -2.48 Fe/g dw).

Safety results of deferasirox 10 mg/kg/day in Study A2209 did not raise any major concerns. Although the incidences of the most commonly reported treatment related AEs (nausea, diarrhoea and rash) were higher in the deferasirox 10 mg/kg/day group compared to the 5 mg/kg/day group (nausea: 7.3% versus 5.5%; diarrhoea: 9.1% versus 0.0%; rash: 9.1% versus 3.5%) and there were dose dependent increases in serum creatinine over time, this is consistent with the known safety profile of deferasirox as stated in the currently approved PI. The overall incidences of all causality AEs, SAEs, AEs leading to discontinuation, and treatment related AEs were comparable between the 2 deferasirox groups. The incidence of treatment related SAEs in the deferasirox 10 mg/kg/day group was low (1 subject). Although the incidences of gastrointestinal AEs and skin rash were higher in the 10 mg/kg/day compared to the 5 mg/kg/day group, the incidence of AEs related to GI haemorrhage and ulcers or esophagitis in the deferasirox 10 mg/kg/day group was low (1 subject), as was the incidence of rash

persistent for more than 1 week or severe rash (3 subjects). The number of subjects in the deferasirox 10 mg/kg/day group who had GI adverse events that led to interruption of study drug within 10 days of event onset was small (2 subjects) and the duration of these GI events was relatively short (median duration of all GI events in the deferasirox 10 mg/kg/day group was 6.5 days). The incidence of notably abnormal serum creatinine and creatinine clearance in the deferasirox 10 mg/kg/day group was low (3 and 1 subjects, respectively). For the majority of subjects in the deferasirox 10 mg/kg/day group (96.4%) the worst category of post baseline creatinine clearance was greater than or equal to 60mL/min. The overall incidence of any treatment related AEs related to renal function in the deferasirox 10 mg/kg/day group was also low (1 event of increased serum creatinine). The proportion of subjects with a shift to a maximum post baseline AST or ALT of greater than 2.5 times ULN from a baseline AST or ALT of lower grades was low in the deferasirox 10 mg/kg/day group (3 subjects [5.5%] and 6 subjects [10.9%] for AST and ALT, respectively), as was the incidence of notably abnormal transaminases in the deferasirox 10 mg/kg/day group (1 subject), and the incidence of treatment related AEs related to hepatic function (1 event of an increase in ALT). Analyses of haematological parameters did not raise any safety concerns in the deferasirox 10 mg/kg/day group, and there were no incidences of AEs related to hearing loss or to lens opacities, retinal changes and optic neuritis in the deferasirox 10 mg/kg/day group.

With regards to the benefit risk profile in the paediatric population aged 10 to less than 18 years, efficacy and safety analyses in the age subgroups less than 18 years and greater than or equal to 18 years in Study A2209 did not raise any major concerns, although the overall small sample size of subjects less than 18 years of age made interpretation difficult. Efficacy analyses results with reference to the absolute change from baseline in LIC at Week 52 (primary endpoint), were comparable between the paediatric subgroup (aged less than 18 years) and those greater than or equal to 18 years in the deferasirox 5 mg/kg/day group (-1.55 and -1.81 mg Fe/g dw in age groups of less than 18 years and greater than or equal to 18 years, respectively) as well as in the deferasirox 10 mg/kg/day group (-3.28 and -3.86 mg Fe/g dw, respectively). Safety analyses of the incidence of AEs, severe AEs, treatment-related AEs and AEs leading to permanent study drug discontinuation in the subgroups of subjects aged less than 18 versus greater than or equal to 18 years did not raise any safety concerns. In particular, no subjects less than 18 years of age in the study had notably abnormal serum creatinine, creatinine clearance, UPCR, ALT, AST or absolute neutrophil count. It is also noted that deferasirox is currently approved for use in paediatric patients aged 2 and above with transfusional iron overload.

## 10. First round recommendation regarding authorisation

It is recommended that the application for extension of indication of deferasirox for treatment of chronic iron overload in patients with non-transfusion dependent thalassaemia syndromes aged 10 years and older be approved.

This is subject to a satisfactory response to the clinical questions raised, as well as submission to the TGA of the data for the extension part of Study A2209 when it is completed.

## 11. Clinical questions

### 11.1. Pharmacokinetics

- Please clarify the inclusion/exclusion criteria for Study A2125 with reference to platelet count levels.

**Rationale for question:** As commented, the study protocol and CSR of A2125 has stated that subjects in the healthy control group had to have platelet count greater than 50000 x 10<sup>9</sup>/L at screening and baseline, and those with severe hepatic impairment had to have platelet count greater than 30000 x 10<sup>9</sup>/L at screening and baseline. It is unclear if the sponsor had meant greater than 50 x 10<sup>9</sup>/L and greater than 30 x 10<sup>9</sup>/L, respectively.

## 11.2. Pharmacodynamics

Not applicable.

## 11.3. Efficacy

- Please clarify the criterion for dose doubling at Week 24 in Study A2209.

**Rationale for question:** As commented, the CSR for Study A2209 is inconsistent in stating the criterion for dose doubling at Week 24 with regards to absolute LIC level, stating it as LIC greater than or equal to 7 mg Fe/g dw in some instances or sections and LIC greater than 7 mg Fe/g dw in others. For example, the criterion was stated as '*LIC greater than or equal to 7 mg Fe/g dw*' in the methodology section of the synopsis, presentation of efficacy results in the synopsis, and other sections but as '*LIC greater than 7 mg Fe/g dw*' in other sections.

- Please elaborate on the reasoning and rationale for selecting the respective serum ferritin threshold levels for predicting the LIC levels.

**Rationale for question:** The sponsor stated that

*'Chelation therapy should only be initiated when there is evidence of iron overload (liver iron concentration (LIC) greater than or equal to 5 mg Fe/g dry weight (dw) or serum ferritin consistently greater than 800 microgram/L),'* and

*'Every 3 to 6 months of treatment, consider a dose increase in increments of 5 to 10 mg/kg if the patient's LIC is greater than or equal to 7 mg Fe/g dw, or serum ferritin is consistently greater than 2,000 microgram/L and not showing a downward trend, and the patient is tolerating the drug well',*

and that

*'Once a satisfactory body iron level has been achieved (LIC less than 3 mg Fe/g dw or serum ferritin less than 300 microgram/L), treatment should be interrupted.'*

The corresponding serum ferritin thresholds are based on additional Receiver Operating Characteristic (ROC) analyses on the correlation between LIC and serum ferritin. However, the sponsor, in the presentation of the results of these analyses and its conclusion, did not elaborate on the reason for selecting the particular serum ferritin threshold levels, apart from citing the positive and negative predictive values (PPV and NPV, respectively). It is unclear to the evaluator, for example, why serum ferritin greater than 2000 µg/L had been chosen as a threshold level for predicting LIC greater than or equal to 7 mg Fe/g dw, instead of, say 1900 µg/L (PPV of 94%) or 1800 µg/L (PPV of 95%).

## 11.4. Safety

- Please provide results of the echocardiography tests done in Study A2209

**Rationale for question:** Echocardiography was performed at screening and at end of study visit. However, the results were not presented in the CSR. It is unclear to the evaluator if this is to be taken to mean that there were no new or worsened clinically significant abnormalities found in the echocardiography tests.

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## 12. References

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