



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for deferasirox

Proprietary Product Name: Exjade

Sponsor: Novartis Pharmaceuticals Australia Pty
Ltd

March 2014

TGA Health Safety
Regulation

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- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
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- The work of the TGA is based on applying scientific and clinical expertise to decision making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
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- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Extension of indications
<i>Decision:</i>	Approved
<i>Date of decision:</i>	24 October 2014
<i>Active ingredient:</i>	Deferasirox
<i>Product name:</i>	Exjade
<i>Sponsor's name and address:</i>	Novartis Pharmaceuticals Australia Pty Ltd 54 Waterloo Road North Ryde NSW 2113
<i>Dose form:</i>	Dispersible tablet
<i>Strength(s):</i>	125 mg, 250 mg and 500 mg
<i>Container(s):</i>	Blister pack
<i>Pack size(s):</i>	28 tablets, 84 tablets (for each strength)
<i>Approved therapeutic use:</i>	<p>The treatment of chronic iron overload due to blood transfusions (transfusional haemosiderosis) in adults and paediatric patients 6 years and older.</p> <p>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.</p> <p>Exjade is also indicated for the treatment of chronic iron overload in patients with non transfusion dependent thalassaemia syndromes aged 10 years and older.</p>
<i>Route of administration:</i>	Oral
<i>Dosage:</i>	The dose regimen for the additional indication of iron overload in patients with non transfusion dependent thalassaemia (NTDT) is a recommended initial daily dose of deferasirox of 10 mg/kg body weight.
<i>ARTG number (s):</i>	119230, 119231 and 119232

Product background

Deferasirox is an orally active N-substituted bis-hydroxyphenyl-triazole tridentate iron chelating agent. The sponsor has stated that deferasirox is highly selective for iron and

that it binds iron with high affinity in a 2 to 1 ratio. Deferasirox promotes excretion of iron, primarily in the faeces.

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 iron overload in NTDT often becomes significant in the second decade of life and is very rare in children under 10 yrs of age. Phlebotomy is contraindicated due to underlying anaemia.

The sponsor is 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.

Currently, Exjade is registered for the following indication:

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 AusPAR describes the application by the sponsor to register Exjade for the additional indication:

for the treatment of chronic iron overload in patients with nontransfusion dependent thalassaemia syndromes aged 10 years and older.

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 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.

Regulatory status

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

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) as a new chemical entity in 2006.

Other agents in the class and registered in Australia include Desferal (desferrioxamine) and Ferriprox (deferiprone). In Australia, neither Desferal nor Ferriprox is approved for the indication of iron overload in patients with NTDT.

At the time TGA considered this application a similar application had been approved in the European Union (EU) for the indication:

treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients aged 10 years and older with non transfusion dependent thalassaemia (NTDT) syndromes.

A similar application was also approved in the United States of America (USA) in May 2013 for the use of Exjade for the indication:

Exjade is indicated for the treatment of chronic iron overload in patients 10 years of age and older with non transfusion dependent thalassaemia syndromes and with a liver iron (Fe) concentration (LIC) of at least 5 mg Fe per gram of dry weight (dw) and a serum ferritin greater than 300 mcg/L. This indication is based on achievement of an LIC less than 5 mg Fe/g dw. An improvement in survival or disease related symptoms has not been established.

The second line indication is not relevant in Australia, where use of deferoxamine for treatment of iron overload in patients with NTDT is not approved.

It is noted that the USA and EU submissions included a '120 day safety and efficacy update' for the pivotal Study A2209, that was not in the Australian submission. The USA also has additional data regarding the magnetic resonance imaging (MRI) technique for determination of liver iron concentration.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a quality evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Contents of the clinical dossier

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 DI 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 to II study in patients with iron overload resulting from hereditary haemochromatosis, will be evaluated as a supporting efficacy/safety study.

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.

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.¹

Pharmacokinetics**Studies providing pharmacokinetics data**

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

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.

Summary of pharmacokinetics (PK)***Pharmacokinetics in other special populations****Pharmacokinetics in subjects with impaired hepatic function*

Results in Study A2125 showed that, compared to the healthy control group, deferasirox area under the curve from time zero to infinity (AUC_{inf}) was increased by 16% in the mild hepatic impairment group and by 76% in the moderate hepatic impairment group, while C_{max} 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.

Pharmacokinetic interactions*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_{max} , when midazolam was administered with deferasirox, compared to when midazolam was administered alone.

¹ European Medicines Agency, "ICH Topic E 6 (R1) Guideline for Good Clinical Practice Step 5: Note for guidance on good clinical practice (CPMP/ICH/135/95)", July 2002, Web, accessed 6 February 2014 <www.edctp.org/fileadmin/documents/EMEA_ICH-GCP_Guidelines_July_2002.pdf>

Results in Study A2129 showed that co administration of cholestyramine reduced deferasirox exposure by 45% and C_{max} 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.

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.

Pharmacodynamics

Not applicable

Efficacy

Studies providing efficacy data

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

Pivotal efficacy studies

Study A2209

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 USA. 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.

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 evaluator considered that 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 search² 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.

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 baseline³), 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

² 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.

³ 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.

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.

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

Efficacy variables and outcomes

The primary efficacy variable was the absolute change from baseline in LIC⁴ 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,⁵ correlation between serum ferritin and LIC, efficacy of dose doubling, and analyses of exploratory haematological and iron metabolism parameters.⁶

Comments: Overall, the evaluator considered that 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.

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

⁴ Liver iron content was estimated throughout the study by the use of a magnetic resonance imaging technique called R2-MRI.

⁵ 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.

⁶ 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)

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.

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 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.

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.

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 up 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

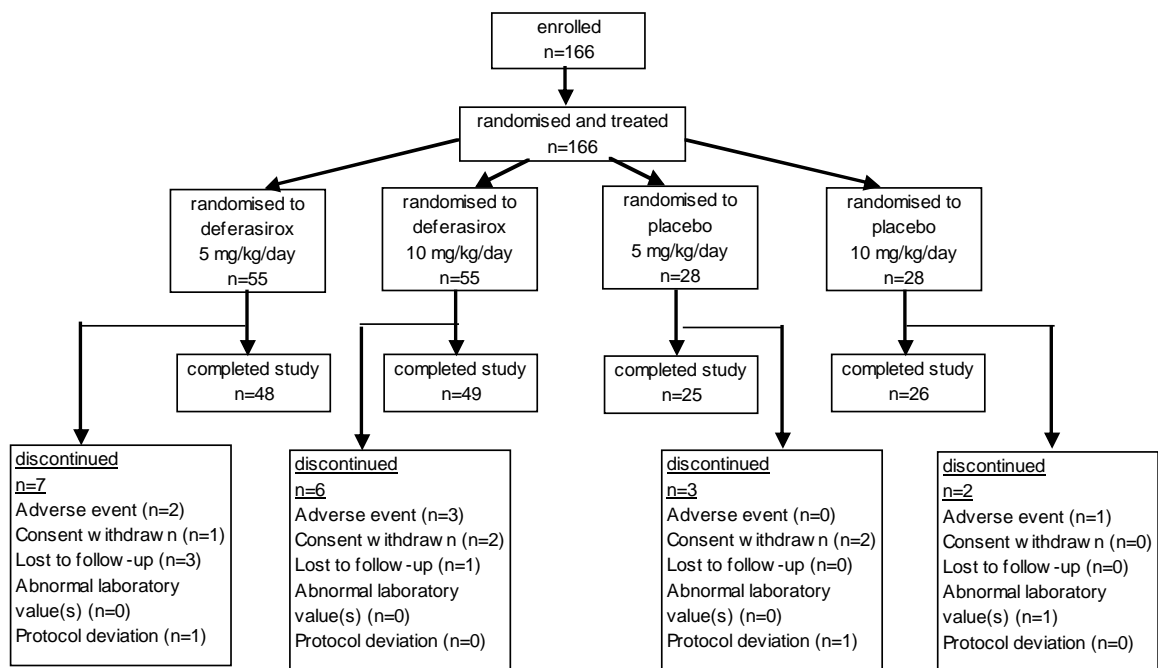
- baseline serum ferritin
 - greater than 300 up to 500 µg/L
 - greater than 500 up to 1000 µg/L
 - greater than 1000 µg/L, and
- splenectomy (yes, no)
- An additional ad hoc analysis was performed for absolute change from baseline in LIC at Week 52 by subgroup of underlying disease (beta thalassaemia, 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.

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

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 out of 55], 63.6% [35 out of 55] and 58.9% [33 out of 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).

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: The evaluator 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.

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.

Results for other efficacy outcomes

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]).

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 up 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 up to 500 µg/L
 - greater than 500 up to 1000 µg/L
 - greater than 1000 µg/L
- 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 17.5 mg/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 7.5 mg/kg/day (-1.72 mg Fe/g dw).

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 µg/L versus 114.54 µg/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 µg/L versus 114.54 µg/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.

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.

Other efficacy studies

Study A2202

Study A2202 was a Phase I to II open label, dose escalation multi centre⁷ 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.⁸ 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.

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).⁹ 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 month 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

⁷ 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).

⁸ 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.

⁹ 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.

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.¹⁰ 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.

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,

¹⁰ 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.

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/m², 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 weeks 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 time points, 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.

Analyses performed across trials (pooled analyses and meta analyses)

Not applicable.

Evaluator's overall conclusions on 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. 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 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,¹¹ 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.¹²

Safety

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; gastrointestinal (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.

Auditory and ophthalmologic examinations¹³ were performed during screening and after 12 months (that is, Week 52). Significant findings of the auditory and ophthalmologic

¹¹ 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.

¹² 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

¹³ The ophthalmologic examination included visual acuity test, tonometry, slit lamp examination of anterior segment, and slit lamp examination of the lens.

examinations that met the definition of an adverse event (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.

Pivotal studies that assessed safety as a primary outcome

Not applicable.

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.

Pivotal studies that assessed safety as a primary outcome

Not applicable.

Summary of 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 study¹⁴ 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.

¹⁴ 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.

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.

Evaluator's overall conclusions on safety

Overall, the safety results of the pivotal Study A2209 were consistent with the known safety profile¹⁵ and adverse effects (AEs) of deferasirox. In Study A2209, the incidences of all causality AEs, serious adverse events (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%).

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. 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), 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

¹⁵ For the purposes of this document 'known safety profile' is to mean 'known safety profile of deferasirox as stated in the currently approved PI'.

clearance (n=2; 1 each in the deferasirox 5 and 10 mg/kg/day groups) or urinary protein/creatinine ration (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. The proportion of subjects with a shift to a maximum post baseline AST of greater than 2.5 times upper limit normal (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 here 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 Absolute neutrophil count (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 this submission 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, 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.

First round benefit-risk assessment

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

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. 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 60 mL/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. 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).

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 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. 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.

The 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.

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.

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.

List of questions

Clinical questions

Pharmacokinetics

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

Rational 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 $50000 \times 10^9/L$ at screening and baseline, and those with severe hepatic impairment had to have platelet count greater than $30000 \times 10^9/L$ at screening and baseline. It is unclear if the sponsor had meant greater than $50 \times 10^9/L$ and greater than $30 \times 10^9/L$, respectively.

Response from sponsor: Indeed the additional inclusion criteria for platelets in the protocol and CSR of A2125 study for patients in groups 1, 2 and 3 (healthy controls and patients with mild and moderate hepatic impairment) and those in group 4 (severe hepatic impairment) was written as greater than $50,000 \times 10^9/L$ and greater than $30,000 \times 10^9/L$ at screening and baseline, respectively. However, what was meant was greater than $50 \times 10^9/L$ and greater than $30 \times 10^9/L$, respectively.

Pharmacodynamics

Not applicable.

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.

Response from sponsor: Dose doubling in Study A2209, which was introduced in Amendment 2 (14 August 2009), was according to the following criteria:

- Patients with a LIC greater than 7 mg Fe/g dw after 6 months of treatment and with a LIC reduction by less than 15% compared to baseline had their treatment dose doubled

- Patients with a LIC greater than 7 mg Fe/g dw after 6 months of treatment and with a LIC reduction by 15% or more compared to baseline kept the same dose of treatment
- Patients with a LIC equal to or lower than 7 mg stayed on the same dose

As such, these were the criteria that were followed during the execution of the study and the mentioning of '*LIC greater than or equal to 7 mg Fe/g dw*' in some sections of the CSR or the synopsis was inadvertently done.

- 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 µg/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%).

Response from sponsor: The corresponding serum ferritin thresholds are based on additional Receiver Operating Characteristic (ROC) analyses on the correlation between LIC and serum ferritin.

To develop serum ferritin (SF) guidance for the proposed label, a ROC analysis was conducted using all screened subjects from study A2209 with both a LIC and SF value (n=282). The objective was to identify the SF threshold that would balance the risk/benefit of using chelation therapy that is to minimize the proportion of patients treated despite LIC of less than 5 mg Fe/g dw without substantially increasing the proportion of patients who would not be treated despite an LIC greater than or equal to 5 mg Fe/g dw. In order to achieve this goal, the following measures were calculated.

- The Positive Predictive Value (PPV): The likelihood that a patient with SF greater than a specific threshold will also have LIC greater than or equal to the desired threshold. For patients with higher iron burden where chelation is critical, the higher the PPV for a specific threshold of SF, the greater the likelihood that the patient will have a high LIC, and hence be a candidate for chelation.
- The Negative Predictive Values (NPV): The likelihood that a patient with SF lower than a specific threshold will also have an LIC lower than to equal to the desired threshold. Thus, for patients with lower iron burden where over-chelation is of concern, the higher the NPV for a specific threshold of low SF, the greater the likelihood that the patient will have a lower LIC, and hence should stop chelation therapy.

Using the data from the ROC analysis and applying it to the serum ferritin recommendations proposed, the proportion of patients that would be correctly treated, as well as those that could be “missed” can be calculated.

Recommendation to start treatment when SF > 800 µg/L: With the recommendation to start treatment when SF greater than 800 µg/L, 91.7% (PPV) of patients have an LIC greater than or equal to 5 mg Fe/g dw, and 98.7% (PPV) of patients have an LIC greater than or equal to 3 mg Fe/g dw. Conversely, 46.4% (1-NPV) of patients will have an LIC greater than or equal to 5 mg Fe/g dw, but a SF less than 800 µg/L and will be “missed” for treatment until their SF increases to greater than 800 µg/L. The serum ferritin cut off of 800 µg/L conservatively balances the risk of chelating patient with low LICs (1.3% of patients have a LIC less than 3 mg Fe/g dw) against the risk of missing patients who should be treated. The conservative approach is recommended as patients with higher LICs and serum ferritin less than 800 µg/L will presumably increase their SF over time and become eligible for treatment.

Recommendations for Dose Escalation: The LIC threshold of greater than 7 mg Fe/g dw for dose increase is consistent with what was used in study A2209. The SF threshold of 2000 µg/L has been determined by the ROC analysis that shows that SF of 2100 µg/L (the next cut off greater than 2000 µg/L in the analysis) is hundred percent predictive (PPV of 100%) of an LIC greater than or equal to 7 mg Fe/g dw, which indicates that a SF value greater than 2000 µg/L can be considered as an adequate threshold above which patients can be dose escalated. In patients in whom LIC was not assessed and SF is less than or equal to 2000 µg/L, a conservative approach is proposed where a dose exceeding 10 mg/kg/day is not to be used. At a SF greater than 2100 µg/L, no patient would have a LIC less than 3 mg Fe/g dw. For patients in whom the dose was increased to greater than 10 mg/kg, dose reduction is recommended to 10 mg/kg when LIC is less than or equal to 7 mg Fe/g dw or serum ferritin is less than or equal to 2000 µg/L. This recommendation is consistent with study A2209 protocol and its extension, where the maximum dose was 10 mg Fe/g dw for an LIC less than 7 mg Fe/g dw and is consistent with the findings of the ROC analysis

Recommendation for dose interruption : The recommendation to stop treatment at LIC less than 3 mg Fe/g dw is consistent with the threshold used in study A2209. In study A2209, a SF threshold of 100 µg/L was used as a safety stopping measure. The SF threshold of 300 µg/L proposed for the prescribing information is more conservative to mitigate against the risk of over chelation and is derived from a ROC analysis showing that 80% (NPV) of patients with SF less than 300 µg/L had a LIC less than 3 mg Fe/g dw and 86.7% (NPV) have a LIC less than 5 mg Fe/g dw, which makes a SF of 300 µg/L an adequate and safe threshold to stop iron chelation therapy.

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.

Response from sponsor: Numerous published studies have shown that patients with NTDT do not have cardiac iron overload despite considerably high liver iron concentration levels. As such, echocardiography was only performed in study A2209 at screening and at end of study as part of regular safety monitoring for cardiac adverse events. Echocardiograms were read locally at the site where they were performed and significant findings that meet the definition of an adverse event were recorded in the adverse event summary page of the case report form and reported as such. No quantitative functional or hemodynamic echocardiography data were systematically

collected in the study database. The events were low in frequency and occurred at a similar frequency between the deferasirox and placebo arms.

Second round evaluation of clinical data submitted in response to questions

The sponsor's response to the clinical questions were taken into account by the Delegate when preparing the Delegate's Overview (see AusPAR section on *Overall conclusion and risk/benefit assessment*).

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

The sponsor submitted a Risk Management Plan [EU-RMP Version 7.0 (dated 8 November 2011)], which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of Ongoing safety Concerns which are shown at Table 2

Table 2. Summary of ongoing safety concerns.

Ongoing safety concern	Type
Important identified risks	Increased serum creatinine Acute renal failure Renal tubular disorders Increased liver transaminases Gastrointestinal haemorrhage, ulcers, esophagitis Hearing loss Lens opacities, retinal changes and optic neuritis Serious hepatic impairment
Important potential risks	Hepatic failure Peripheral blood cytopenias
Important missing information	Paediatric use: paediatric patients age 2 up to 6 years Pharmacokinetics in patients with hepatic impairment Use in patients with renal impairment Long term exposure data in non transfusion dependent thalassemia (NTDT) patients

Pharmacovigilance plan

The sponsor has concluded that both routine and advanced pharmacovigilance is required to monitor the specified ongoing risks and potential risks associated with Exjade.

Additional pharmacovigilance monitoring includes

- Prescription Event Monitoring to examine the safety and use of Exjade prescribed in general practice in England, licensed for the treatment of chronic iron overload due to frequent blood transfusions in patients with beta thalassemia major aged 6 years and older, and also for patients with other anaemia's, or aged 2 to 5 years or with beta thalassemia major and iron overload due to infrequent blood transfusions for whom deferoxamine therapy is contraindicated or inadequate has been in place for the past five years. The ongoing status and results of this study have been reported in PSUR's since PSUR number 5.
- Targeted Questionnaire/checklists for the important identified and potential risks (Specific to Australia).
- Clinical Trial Protocol No. C1CL670A2411 - A 5 year observational study (registry) of children aged 2 to less than 6 years at enrolment with transfusional hemosiderosis treated with deferasirox. The surveillance study will monitor patient safety in actual practice settings, thereby increasing knowledge about the incidence and management of relevant adverse drug reactions. The findings of this study will be reported in PSUR's.
 - Primary Aim: Evaluate the long term safety of deferasirox in an unselected population of children aged 2 to less than 6 years at enrolment with chronic iron overload related to blood transfusions used in the treatment of transfusion dependent anaemias.
 - Secondary Aim: Evaluate the long term effectiveness of deferasirox in this population by collection and analysis of monthly serum ferritin levels over a period of 5 years.

The sponsor is requested to provide the TGA with an update regarding the study.

The evaluator has no objection to the specified pharmacovigilance plan.

Risk minimisation activities

The routine risk minimisation activities described are considered satisfactory.

Additional risk minimisation activities are outlined below.

Novartis has

- Developed educational materials for haematologists and patients and updated them in accordance with the updates to the Australian approved PI.
- Sponsored educational forums for haematologists to learn about the safe and effective use of Exjade within the approved indication.
- Provided a patient support programme since July 2008. The aim of this programme is to educate and enhance compliance through counselling by trained nurses. The programme is available to any patient that consents to participate. The patients receive phone calls at time points tailored to assist patients with understanding iron overload and the need for chelation therapy.
- Australian specific product labelling is in place for all important identified risks and important potential risks.

Summary of recommendations

The following table provides a summary of the OPR evaluation of the RMP issues raised with the sponsor, sponsors responses and OPR evaluation of these responses.

Table 3. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment						
<p>Could the sponsor confirm that educational materials and material for forums will reflect the new indication and safety concerns with respect to hepatic impairment and that the patient support programs will also be updated.</p>	<p>Novartis confirms educational material and patient support programs will be updated in line with the approved NTDT indication. Safety concerns with respect to hepatic impairment are featured in the submitted PI and educational material and patient support programs are aligned to the approved PI.</p>	<p>This is acceptable</p>						
<p>Please provide an update on Clinical Trial Protocol No. CICL670A2411 and the PEM study</p> <p>Rationale for question: As the last PSUR received by the TGA is for the period Nov 2008 to April 2009, the sponsor is requested to provide the TGA with an update regarding the study associated with Clinical Trial Protocol No. CICL670A2411 and the Prescription Event Monitoring (PEM study).</p>	<p>Please refer to 'Status and results of the surveillance program (sentinel site monitoring, paediatric registry) in each Member State (FUM 017)' in Module [1.0.2] for an update on Study CICL670A2411.</p> <p>Within the EU/EEA, participation was open to any physician or any site; the physician information pack distributed at the launch of Exjade in each Member State informs physicians that the safety database of Exjade is limited, and encourages them to enrol patients in the sentinel site monitoring and paediatric registry to increase knowledge about the incidence of important ADRs. ENTRUST has enrolled the first patient in the USA in May 2007. The enrolment is now closed with 269 patients enrolled in the paediatric registry of which 73 are from European countries. This is in excess of the original sample size proposed in the first Risk Management Plan for Exjade ('A total of 200 newly starting Exjade will be enrolled to yield approximately 100 evaluable subjects at the end of 5 years.'). Additional patients were included to replace the ones discontinued early and for which there was less than 6 months data. A few extra patients were also enrolled for ethical reasons related to having already signed patient informed consent prior to the enrolment deadline. The full analysis set (FAS) for this report contains 264 of the 269 enrolled patients since 5 patients did not have drug administration data at baseline (either because it was not yet entered in the eCRF or because there was a query open on that data at the time of the snapshot). For this interim snapshot, the data sets contained 264 patients in the FAS, 263 patients in the Safety set, 226 patients each in the Safety sets 1 and 2</p> <table border="0" data-bbox="555 1197 1064 1332"> <tr> <td>Completed the study</td> <td>33 (12.5%)</td> </tr> <tr> <td>Ongoing</td> <td>134 (50.8%)</td> </tr> <tr> <td>Discontinued study</td> <td>97 (36.7%)</td> </tr> </table>	Completed the study	33 (12.5%)	Ongoing	134 (50.8%)	Discontinued study	97 (36.7%)	<p>This is acceptable.</p>
Completed the study	33 (12.5%)							
Ongoing	134 (50.8%)							
Discontinued study	97 (36.7%)							

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
<p>Please provide an update on Clinical Trial Protocol No. C1CL670A2411 and the PEM study</p> <p>Rationale for question: As the last PSUR received by the TGA is for the period Nov 2008 to April 2009, the sponsor is requested to provide the TGA with an update regarding the study associated with Clinical Trial Protocol No. C1CL670A2411 and the Prescription Event Monitoring (PEM study).</p>	<p>The Drug Safety Research Trust is a UK registered independent charity (No. 327206) operating in association with the University of Portsmouth. Prescription Event Monitoring (PEM), which was established in 1980, is one of the principal activities of the Drug Safety Research Unit (DSRU). PEM is a records based observational cohort form of post marketing surveillance.</p> <p>A Prescription Event Monitoring (PEM) study is being carried out by the Drug Safety Research Unit (DSRU), to examine the safety and use of deferasirox prescribed in general practice in England. Deferasirox is licensed as a treatment of chronic iron overload due to frequent blood transfusions (greater than 7mL/kg/month of packed red blood cells) in patients with beta thalassaemia major aged six years and older. It is also licensed for treatment of chronic iron overload due to blood transfusions when desferioxamine therapy is contraindicated, in patients with other anaemias, in patients aged two to five years and in patients with beta thalassaemia major with iron overload due to infrequent transfusions (less than 7mL/kg/month of packed red blood cells). Prescription data were initially collected for prescriptions issued between September 2006 and February 2007. Following discussions with Novartis Europharm Limited, prescription collection was cancelled for two time periods. Most recently, data collection was resumed in December 2008, as per company request and continues to date. The fifth interim report is based on data derived from Green Form questionnaires as of a data lock of April 2012; the valid cohort consists of 75 patients.</p> <p>The median age of the whole interim 5 cohort was 22 years (IQR 12 to 50 years). The median age for male patients was 19 years (IQR 11 to 42); and for female patients the median age is 26 years (IQR 13 to 56). Forty one patients (54.7% of cohort) were male and 34 (45.3 % of cohort) were female. The most frequently reported indication (16 patients) was for the treatment of iron overload in patients with beta thalassaemia. Primary indications for prescribing deferasirox below for all reported indications); eight of these sixteen patients had frequent blood transfusions (greater than 7mL/kg/month of packed red blood cells) for beta thalassaemia, (21.3% of the total interim 5 cohort, 26.7% of the 60 patients for whom the indication was reported).</p> <p>Of the 35 patients for whom the initial dose of deferasirox was reported in this cohort, the majority of patients (30, 85.7%) were prescribed either 10 mg/kg/day or 20 mg/kg/day. Treatment was initiated by a specialist for 57 patients (76.0% of cohort, 96.6% of those for whom it was specified who initiated treatment) and by their GP for only two patients (2.7% of cohort; 3.4% of those for whom it was specified who initiated treatment). For the remaining sixteen patients (21.3% of cohort), it was not specified who started the treatment with deferasirox. For 35 (46.7%) of the 75 patients in the cohort, the GP provided a definitive opinion about the effectiveness of deferasirox. In 32 of these 35 reports, it was recorded that</p>	<p>This is acceptable.</p>

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	<p>reaction to deferasirox and this related to an abnormal renal function test. This event was reported in a 75 year old female patient and has been followed up.</p> <p>GPs recorded fifteen reasons for stopping deferasirox in thirteen patients (17.3% of the whole interim 5 cohort). Clinical events reported as the reason for stopping treatment included raised blood creatinine, reduced visual acuity, gastritis, abdominal pain and arthralgia. Three of these events were followed up for further information (reduced visual acuity, increased blood creatine, and arthralgia). Of the 75 patients, 26 were reported to have had their serum creatinine measured prior to treatment with deferasirox (34.7% of cohort). This was not known or not specified for the majority of the cohort (46 patients, 61.3%). Of the 26 patients for whom serum creatinine was measured, values were provided for 17 patients; of these only ten were recorded prior to starting treatment with deferasirox. The median value for creatinine was 82 µmol/L, with an interquartile range of 69 to 116 µmol/L. Where information on use of an iron chelating agent in the twelve months prior to starting deferasirox was requested, a definitive response was received for 34 patients (45.3% of cohort). Of these 34 patients, 23 were reported to have used such products and the remaining 11 patients had not.</p> <p>Only one patient was reported to have used another iron chelating agent during treatment with deferasirox; 37 patients had not used another agent during treatment and for a further 37 patients this was either unknown or unspecified. In total, sixty three adverse events deemed unrelated to deferasirox treatment by the investigator were reported for 25 of the 75 patients in the cohort. As of the data lock for the fifth interim report, there have been eight events followed up in seven patients</p> <p>Due to the nature of the use of the product (by specialists), the data available to the DSRU have been and will continue to be limited.</p>	

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Introduction

NTDT involves iron overload via increased intestinal absorption (driven, via down regulation of hepcidin, by anaemia due to ineffective haematopoiesis) despite few transfusions. The chelation treatment regimen for NTDT patients is different from that established for transfusional iron overload due to a lower rate of ongoing iron accumulation. Iron overload in NTDT often becomes significant in the second decade of life and is very rare in children under 10 yrs of age. Phlebotomy is contraindicated due to underlying anaemia.

Deferasirox is an orally active iron chelating agent. It promotes excretion of iron, primarily in faeces.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical evaluator supported the extension of indication as proposed by the sponsor.

Overview of data

Five clinical studies were provided for review:

PK Study A2125 evaluated use of deferasirox in subjects with hepatic impairment.

Study A2126 was a study of interaction between deferasirox and midazolam. Study A2129 was a study of interaction between deferasirox and cholestyramine.

The pivotal study for the extension of indication was Study A2209 in NTDT patients with iron overload. Study A2202 was a study in hereditary haemochromatosis patients and was considered supportive (but was not relevant for efficacy).

Pharmacokinetics (PK)

The evaluator states of the study in hepatic impairment:

Results in Study A2125 showed that, compared to the healthy control group, deferasirox area under the time curve from time zero to infinity (AUC_{inf}) was increased by 16% in the mild hepatic impairment group and by 76% in the moderate hepatic impairment group, while C_{max} was increased by 22% in both the mild and the moderate hepatic impairment groups.

The evaluator endorses the sponsor's proposed changes to the PI based on this study.

One patient with severe impairment was included in Study A2125. That patient had a pronounced increase in deferasirox exposure. The proposed PI notes that Exjade should not be used in patients with severe hepatic impairment.

Efficacy

Study A2209

This was a randomised, double blind, placebo controlled study in NTDT patients with iron overload. Patients were enrolled from 9 countries across the world. The study was conducted from 2008 to 2011.

Patients were to be 10 years of age or older, with NTDT syndromes, with no transfusion in the 6 months prior to study entry, with LIC greater than or equal to 5 mg Fe/g dw (as measured by R2-MRI) and with serum ferritin greater than 300 µg/L at screening.

The randomised starting dose of deferasirox or placebo was either 5 mg/kg/day or 10 mg/kg/day; doses could double if response at 24 weeks was inadequate, and treatment was to be paused if week 24 LIC was less than 3 mg Fe/g dw, or if this LIC threshold was met after serum ferritin fell to less than 100 µg/L at any visit. Treatment was for 52 weeks (an open label extension phase was not submitted for evaluation).

166 subjects were enrolled: 55 in the 5 mg/kg/day group, 55 in the 10 mg/kg/day group and 56 in total in the two placebo groups. Baseline characteristics were similar across the 3 groups. About 53 to 57% of subjects were male; 55 to 61% were Caucasian; mean age was 31 to 33 yrs. 55 to 61% had beta thalassaemia intermedia; 82 to 91% had previous transfusions; and 61 to 82% had no prior chelation. Baseline mean LIC values were 13.1, 14.6 and 15.9 mg Fe/g dw in the 5 mg/kg/day, 10 mg/kg/day and pooled placebo arms, respectively. Baseline mean serum ferritin was 1141, 1174 and 1305 µg/L respectively. There were 6 out of 55, 7 out of 55 and 8 out of 56 subjects respectively less than 18 yrs.

Primary efficacy outcome

The primary efficacy variable was absolute change from baseline in LIC at week 52, in the intention to treat cohort. Mean change from baseline at 52 weeks was -1.95 mg Fe/g dw in the 5 mg/kg/day group, -3.80 mg Fe/g dw in the 10 mg/kg/day group and +0.38 mg Fe/g dw in the pooled placebo group. Results in both active treatment arms were statistically significantly different from placebo, and results in the 10 mg/kg/day group were statistically significantly different from the lower dose group.

Other efficacy outcomes

Subgroup analysis of patients less than 18 years of age showed outcomes comparable to the whole patient population in this group.

Patients whose dose was increased from 10 to 20 mg/kg/day at week 24 had larger responses than patients on 10 mg/kg/day, but a dose increase from 5 to 10 mg/kg/day at week 24 had little effect which is altogether broadly consistent with a dose response effect.

Results for absolute change in LIC at Week 24 were less impressive, with no significant differences across arms.

Effects on serum ferritin followed the pattern noted above for the primary endpoint. Correlation between change in LIC from baseline to Week 52 and change in serum ferritin from baseline to week 52 was weak ($r=0.311$).

The sponsor studied whether serum ferritin can be used as a monitoring tool to predict LIC, for the purpose of deciding when to start and when to stop chelation.

Study A2202

This was a Phase I to II, open label, dose escalation study in 49 patients with iron overload from hereditary haemochromatosis, and is irrelevant for the proposed new indication.

Safety

Mean duration of exposure was 11.4 to 11.8 months across arms in A2209; 89 to 95% of subjects had 9+ months of exposure.

There were no deaths in A2209. Anaemia was reported as an SAE in 1/55, 2/55 and 0/56 respectively. One subject had positive rechallenge for pruritus and rash in the 10 mg/kg/day group.

AEs that occurred at higher incidence in 5 and 10 mg/kg/day deferasirox groups compared to placebo 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).

The most commonly reported treatment related AEs in the deferasirox 10 mg/kg/day group were diarrhoea (0.0%, 9.1% and 1.8% in the 5 mg/kg/day, 10 mg/kg/day, and pooled placebo groups, respectively) and rash (3.6%, 9.1% and 1.8%, respectively).

Three subjects in A2209, all in the 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. 2 of these 3 patients had relatively low iron burden, with serum ferritin close to 300 µg/mL. One patient developed proteinuria leading to drug discontinuation; proteinuria was ongoing. There was evidence of a modest effect on kidney function with deferasirox at 10 mg/kg/day. 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 5 mg/kg/day group and the pooled placebo group, and were smaller compared to those in the 10 mg/kg/day group.

In A2209, AEs of most interest were:

- The apparent effect on kidney function noted above.
- An AE of hepatotoxicity (jaundice, right upper quadrant pain) after one year on deferasirox, that did not resolve. Given the small sample size, the presence of such an AE is of some concern, although effects on transaminases were not concerning. Fulminant hepatic failure has been reported previously with Exjade. Monitoring is already recommended in the PI.
- One deferasirox subject who experienced a worsening cataract.
- Two deferasirox subjects who developed severe or persistent skin rashes.

No subject less than 18 years had abnormal serum creatinine (or other specific AEs of concern), but few children were studied.

The evaluator considered that safety results in A2209 were consistent with the known safety profile of deferasirox.

Risk management plan

The RMP proposed by the sponsor was considered acceptable by the TGA's Office of Product Review (OPR). The version under review was: RMP (Exjade (deferasirox) (version 7.0) dated 8 November 2011. Implementation of this RMP will be a condition of approval.

Risk-benefit analysis

Study A2209 – choice of primary efficacy endpoint

Absolute change from baseline in LIC at Week 52 was the primary efficacy endpoint. The evaluator notes that efficacy endpoints did not include evaluation of survival, relief of symptoms or end organ damage arising from chronic iron overload (a similar observation has been incorporated into the USA indication). The sponsor states:

'In a retrospective review of data from 584 thalassemia intermedia patients, the most common disease related complications were osteoporosis (22.9%), extramedullary hematopoiesis (21.2%), hypogonadism (17.3%), cholelithiasis (17.1%), followed by thrombosis (14%), pulmonary hypertension (11%), abnormal liver function (9.8%), and leg ulcers (7.9%).'

The sponsor argues LIC correlates with morbidity, citing a paper by Musallam *et al*¹⁶ that reports

'an LIC of greater than or equal to 7 was the best thresholds for differentiating the presence and absence of vascular morbidities and LIC greater than or equal to 6 mg Fe/g dw for endocrine / bone morbidities, hence the importance of keeping LIC below those levels.'

Cardiac iron burden was not assessed but there is evidence that cardiac iron overload is not a major issue in NTDT.

Choice of starting dose in NTDT

The proposed starting dose in NTDT is 10 mg/kg/day. This is supported by efficacy outcomes in Study A2209; these outcomes support dose doubling based on assessment of response at Week 24. There is some evidence that toxicity is dose dependent (for example effects on renal function). Without long term follow up, it is difficult to be categorical that long term effects of toxicity at 10 mg/kg/day will be outweighed by the long term benefits of more effective chelation. As the sponsor notes, morbidity studies in a NTDT setting would take a very long time to conduct.

Starting and stopping rules

The sponsor proposes a starting rule requiring LIC greater than or equal to 5 mg Fe/g dw OR serum ferritin (SF) greater than or equal to 800 µg/mL. Therapy is stopped if SF falls to less than 300 µg/mL or if LIC is less than 3 mg Fe/g dw. (For entry into the pivotal study, patients required LIC greater than or equal to 5 mg Fe/g dw AND SF greater than or equal to 300 µg/mL. Treatment was paused if LIC was less than 3 mg Fe/g dw.)

The clinical evaluator raised the concern that while starting and stopping rules were consistent with those used A2209 as far as LIC was concerned, the thresholds used for serum ferritin were based on 'additional analyses'.

Data for ROC analysis were gathered at screening: they do not reflect any treatment effect. This may be significant, for example if chelation had different impacts on LIC and serum ferritin; indeed, the correlation between changes in these parameters was weak, as might be expected given that serum ferritin level vary with inflammation, infection and ascorbate deficiency.

The USA Food and Drug Administration (FDA) has taken a different approach as reflected in the USA PI for Exjade. There, the starting rule required LIC greater than or equal to 5 mg

¹⁶ Musallam KM, Cappellini MD, Wood JC, *et al*, Elevated liver iron concentration is a marker of increased morbidity in patients with beta thalassemia intermedia. *Haematologica*; 96: 1605-12, 2011

Fe/g dw AND serum ferritin greater than or equal to 300 µg/mL. Therapy is stopped if SF falls to less than 300 µg/mL or if LIC is less than 3 mg Fe/g dw.

The sponsor's proposal is that treatment may start on the basis of MRI evidence of liver iron overload OR serum ferritin evidence; but the SF threshold has been set to minimise the risk of starting chelation in those who have low LIC.

On balance, the sponsor's position on this issue was accepted, but the Advisory Committee on Prescription Medicines (ACPM's) advice is asked. It may be relevant for the ACPM to advise about whether any NTDT patients would have LIC determined by MRI in Australia. Another consideration is whether iron toxicity may start to develop in some subjects because they are 'waiting' for SF to rise to 800 µg/mL; many such patients will have distinctly elevated LIC. An alternative to avoid this risk is to mandate the measurement of LIC; but biopsy has attendant risks so this would typically be via MRI in addition to specialised software which is assumed to be considerably more expensive and inconvenient than serum ferritin testing.

Use in children

There were few children in A2209, although those studied had outcomes comparable to adults. It seems reasonable to allow use in children 10 yrs or above, as proposed by the sponsor, but the ACPM's advice is asked. Use in younger children (to treat transfusional haemosiderosis) is already approved

Proposed action

Approval of this extension of indication, as proposed by the sponsor is supported.

Request for ACPM advice

The sponsor's proposed indication was supported.

The ACPM is requested to advise about whether the indication should be modified, in line with aspects of the USA PI. For example:

Exjade is also indicated for the treatment of chronic iron overload in patients with nontransfusion dependent thalassemia syndromes aged 10 years and older. This is based on the surrogate endpoint of reduction in liver iron concentration over 52 weeks as measured by MRI (see CLINICAL TRIALS). An improvement in survival or disease related symptoms has not been established.

This would emphasise that the pivotal clinical study in support of use in NTDT did not assess survival or symptom improvement, and did not include data beyond 52 weeks (assessed by the TGA). The ACPM should note that the proposed PI already includes the following information under Clinical Trials:

Clinical trials to demonstrate increased survival or to confirm clinical benefit have not been completed.

Also, no similar caveat is present for the existing indication; but the patient populations are different.

The committee is requested to provide advice on the following specific issues:

- Should the sponsor's starting / stopping rules based on LIC and serum ferritin thresholds be accepted?
- Should a caveat be added to the indication, noting use of a surrogate endpoint in the pivotal clinical study supporting use in NTDT?

- Given the fairly limited exposure in children, should the indication include children 10 years and older?

The committee is requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Starting and stopping rules based on LIC and serum ferritin

Should the sponsor's starting/stopping rules based on LIC and serum ferritin thresholds be accepted?

Response

Novartis would like to summarise the evidence and rationale behind the proposed thresholds to tailor (start and stop) iron chelation therapy in non transfusion dependent thalassemia (NTDT) patients. Novartis would also like to elaborate on how these thresholds should be appropriately used to guide iron chelation therapy and to ensure a balance whereby patients who require iron chelation therapy do receive it while those who do not require iron chelation therapy are not exposed to it, specifically with regard to the Delegate's consideration whether

iron toxicity may start to develop in some subjects because they are 'waiting' for serum ferritin to rise to 800 µg/mL.

As with the first approval for transfusional iron overload, the primary efficacy evidence was based on LIC because it is the most robust measure of total body iron loading. LIC's clinical utility is limited by the availability of non invasive methods to obtain LIC measures. Serum ferritin is a low cost, globally accessible test and is considered a valid surrogate of LIC to detect iron overload and to guide treatment for iron overload. The association of LIC and SF were assessed as a secondary endpoint of the trial with the specific aim of allowing both measures to guide treatment.

Accordingly, Novartis would like to explain the evidence and rationale of the proposed LIC and corresponding alternate serum ferritin level thresholds to start and stop iron chelation therapy in NTDT greater than

LIC of 5 mg Fe/g dry weight (dw) OR serum ferritin of greater than 800 µg/L to start iron chelation therapy in NTDT

The pivotal Study A0107 in the transfusional iron overload setting used an inclusion threshold of LIC greater than or equal to 2 mg Fe/g dw for iron chelation treatment initiation. In the NTDT pivotal Study A2209, given the lower iron loading rates compared to regularly transfused patients, a more conservative LIC threshold of greater than or equal to 5 mg Fe/g dw was recommended as a criterion to start iron chelation in NTDT by the Study Steering Committee when the study was designed.

More recent data support the use of this threshold (LIC greater than or equal to 5 mg Fe/g dw) to start iron chelation therapy in NTDT patients. An LIC greater than or equal to 6 mg Fe/g dw was found to be the best threshold for discriminating the presence and absence of endocrine/bone morbidity whereby patients with an LIC greater than or equal to 6 mg Fe/g dw were 4.05 times (95% confidence interval (CI): 1.96 to 8.35) more likely to have endocrine/bone morbidity compared with patients with an LIC less than 6 mg Fe/g dw¹⁷.

These findings indicate the importance of keeping LIC less than 6 mg Fe/g dw in patients with NTDT and support the more recent recommendations to lower the LIC treatment

¹⁷ Musallam KM, Cappellini MD, Wood JC, *et al*, Elevated liver iron concentration is a marker of increased morbidity in patients with beta thalassemia intermedia. *Haematologica*; 96: 1605-12, 2011

threshold in this patient population: 'Iron chelation therapy with deferasirox should be initiated in NTDT patients 10 years of age or older if: Liver iron concentration reaches greater than or equal to 5 mg Fe/g dry weight (OR serum ferritin level reaches greater than or equal to 800 ng/ml when liver iron concentration measurement is unavailable).¹⁸

Most recently, it was also demonstrated that NTDT patients with a LIC greater than or equal to 5 mg Fe/g dw have a significantly higher prevalence of single as well as multiple clinical morbidities than patients with a LIC less than 5 mg Fe/g dw (60.2% versus 16.1%, $p < 0.001$). Within a clinically relevant LIC range (3 to 15 mg Fe/g dw), the 5 mg Fe/g dw threshold had the highest absolute risk difference for development of any morbidity (34.7%).¹⁹

Collectively, this evidence supports starting iron chelation therapy in NTDT patients with LIC greater than or equal to 5 mg/g dw to ensure treatment is promptly delivered to such patients at high risk of iron related morbidity. In order to select the appropriate alternate serum ferritin threshold when LIC measurement is not feasible, the correlation of LIC and serum ferritin level in study A2209 was assessed. The correlation between both indices in NTDT ($r = 0.64$ in Study A2209 at baseline) was similar to the correlation noted in regularly transfused thalassemia major patients where the use of serum ferritin to guide chelation therapy is well established ($r = 0.64$ in patients pooled from registration Studies A0106, A0107, and A0108 at baseline).

A Receiver Operating Characteristic (ROC) curve analysis using the screening data from pivotal NTDT study A2209 and including all screened subjects with both a LIC and serum ferritin value ($n = 282$) was done to identify the serum ferritin threshold that would balance the risk/benefit of using chelation therapy, that is, to minimize the proportion of patients treated despite LIC being less than 5 mg Fe/g dw without substantially increasing the proportion of patients who would not be treated despite an LIC greater than or equal to 5 mg Fe/g dw. The recommendation to start treatment when serum ferritin level is greater than 800 $\mu\text{g/L}$, ensures that the majority (91.7%) of patients who should be treated (LIC greater than or equal to 5 mg Fe/g dw) would receive treatment (CSR A2209). This is further supported by analyses from Study A2209 of on treatment values which have confirmed the ROC findings from baseline data. In this new analysis, 130 NTDT patients who completed up to 2 years treatment and had serum ferritin level and LIC measurements at baseline and end of study were included.

Using the same ROC methodology, a serum ferritin level of greater than 800 $\mu\text{g/L}$ was 94.1% predictive of LIC greater than or equal to 5 mg Fe/g dw.²⁰ Thus, the serum ferritin threshold of greater than 800 $\mu\text{g/L}$ conservatively balances the risk of over chelating patients with low LIC against the risk of missing patients who should be treated. We acknowledge the delegate's consideration that 'iron toxicity may start to develop in some subjects because they are "waiting"' but believe that the selected serum ferritin threshold represents the most appropriate benefit-risk balance in this slowly developing condition, based on published information and the data generated in Study A2209.

LIC of less than 3 mg Fe/g dw OR serum ferritin less than 300 $\mu\text{g/L}$ to stop iron chelation therapy in NTDT:

This LIC threshold was selected and used in study A2209 to avoid over chelation of patients. A sub analysis from Study A2209 confirmed that the safety profile of deferasirox

¹⁸ Taher AT, Musallam KM, El-Beshlawy A, Age-related complications in treatment naïve patients with thalassaemia intermedia. *Br J Haematol*; 150: 486-9, 2010

¹⁹ Musallam KM, Cappellini MD, Wood JC, *et al*, Elevated liver iron concentration is a marker of increased morbidity in patients with beta thalassemia intermedia. *Haematologica*; 96: 1605-12, 2011

²⁰ Taher A, Porter J, Viprakasit V, *et al*, Serum ferritin for predicting clinically relevant LIC thresholds to guide management of patients with nontransfusion-dependent thalassemia treated with deferasirox: THALASSA study extension analysis, *Haematologica*; 98: S117, 2011.

remains consistent as NTDT patients approach the target LIC of less than 3 mg Fe/g dw for stopping chelation therapy.²¹ In order to provide an assessment of serum ferritin thresholds that would guide the interruption of iron chelation, the percentage of patients with LIC less than 3, less than 5, and less than 7 mg Fe/g dw at a serum ferritin cut off of 100 µg/L (which was used in the study as a serum ferritin based treatment stopping criterion) and 300 µg/L were calculated. The thresholds for LIC were set as follows: LIC less than 3 mg Fe/g dw as a safety stopping criterion; LIC less than 5 mg Fe/g dw as a criterion below which iron chelation was not started; and LIC less than 7 mg Fe/g dw as a dose below which dose escalation was not done. All 3 patients whose serum ferritin reached less than or equal to 100 µg/L had an LIC less than 3 mg Fe/g dw. At a serum ferritin cut off of 300 µg/L, 12 out of 15 (80%) patients had an LIC less than 3 mg Fe/g dw, 13 out of 15 (87%) patients had an LIC less than 5 mg Fe/g dw, and 15 out of 15 (100%) patients had an LIC less than 7 mg Fe/g dw (CSR A2209) This indicates that a serum ferritin value of 300 µg/L is an adequate and at the same time safe threshold to interrupt iron chelation therapy. This was further confirmed from a similar ROC analysis using on treatment values.²² The shorter monitoring interval using serum ferritin levels (monthly) allows close monitoring of iron burden changes thus ensuring timely treatment interruption. The use of the serum ferritin threshold of 800 µg/L for starting chelation therapy and 300 µg/L to stop chelation therapy in NTDT is further supported by an independent 11 year cohort study presented at the 2013 European Haematology Association Congress,²³ which evaluated serum ferritin levels in relation to morbidity in beta thalassemia intermedia, a sub type of NTDT. The cumulative incidence one of morbidity was 100% for patients with serum ferritin levels of greater than or equal to 800 µg/L, while it was 0% for patients with serum ferritin levels less than or equal to 300 µg/L. In light of this, Novartis proposed the following wording to the Dosing and Administration section of the Australian PI

'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 to stop iron chelation therapy

'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).'

These recommendations are in agreement with the recent Thalassaemia International Federation guidelines for the management of NTDT:

'Iron chelation therapy with deferasirox should be initiated in NTDT patients greater than or equal to 10 years of age if: Liver iron concentration reaches ≥ 5 mg Fe/g dry weight (OR serum ferritin level reaches ≥ 800 ng/ml when liver iron concentration measurement is unavailable)'

and

²¹ Taher A, Porter J, Viprakasit V, *et al*, The Safety Profile of deferasirox remains consistent as non-transfusion-dependent thalassemia (NTDT) patients approach the target liver iron concentration of less than 3 mg fe/g dw for interrupting chelation, *Haematologica*; 98: P391, 2013

²² Taher A, Porter J, Viprakasit V, *et al*, Serum ferritin for predicting clinically relevant LIC thresholds to guide management of patients with nontransfusion-dependent thalassemia treated with deferasirox: THALASSA study extension analysis [abstract]. *Haematologica*; 98(S1): S1171, 2013

²³ Musallam KM, Cappellini MD, Daar S, *et al*, Morbidity risk in untreated patients with β -thalassemia intermedia: a closer look at the role of iron overload [abstract]. *Haematologica*; 98(S1): S1172, 2013

*'deferasirox therapy should be discontinued when patients reach a liver iron concentration value of 3 mg Fe/g dry weight (OR serum ferritin level 300 ng/ml if liver iron concentration measurement is unavailable)'.*²⁴

Endpoint of the study

Should a caveat be added to the indication, noting use of a surrogate endpoint in the pivotal clinical study supporting use in NTDT?

Response

The proposed new indication for deferasirox is based on a randomised, placebo controlled trial Study C1CL760A2209 that successfully met its primary endpoint, defined as the absolute change in LIC from baseline to Week 52. Change in LIC was the basis of the success criteria of iron chelation therapy that were agreed upon with Health Authorities for the deferasirox registration program in transfusional iron overload (in the initial registration studies a decrease of greater than or equal to 3 mg Fe/g dw in LIC was used as success criterion in heavily iron overloaded patients). In addition, the clinical community recognises reductions in LIC as a meaningful endpoint indicative of clinical benefit in patients with thalassemia.²⁵ Novartis acknowledges that the Study A2209 did not evaluate survival or clinical benefit as an efficacy endpoint. This is correctly reflected in the Australian PI at the end of the CLINICAL TRIALS section:

'In clinical trials, Exjade has been shown to reduce liver iron concentration and serum ferritin levels. Clinical trials to demonstrate increased survival or to confirm clinical benefit have not been completed.'

The location of this statement at the end of the clinical trials section indicates it applies to both the approved indication and proposed NTDT indication, hence there is no need to incorporate it into the INDICATION section as well.

Use in children

Given the fairly limited exposure in children should the indication include children 10 years and older?

Response

Study A2209 showed that the safety in paediatric patients is not different from adult patients with NTDT; the safety profile for these patients was similar to that of the overall population (CSR A2209). Longer term data from the completed 1 year extension 2209E (which allowed daily doses of up to 20 mg/kg) have confirmed the safety and efficacy profile of deferasirox in NTDT.

Exjade has been approved for use in children 6 years and older for the treatment of chronic iron overload due to blood transfusions (transfusional haemosiderosis) and also in paediatric patients aged 2 to 5 years who are unable to take desferrioxamine therapy or in whom desferrioxamine has proven ineffective since 2006 in Australia. For that indication, 292 paediatric patients aged 2 to 15 years were enrolled in the four main safety and efficacy studies included in the original registration dossier. Paediatric and adult patients were followed for up to 5 years, including annual growth and development assessments for paediatric subjects. Novartis will also conduct an observational, multi center, study (Study C1CL670E2422) to confirm the long term safety profile of deferasirox in the treatment of paediatric patients (age greater than or equal to 10 to less than 18) with nontransfusion dependent iron overload with exposure up to 5 years in

²⁴ Taher A, Vichinsky E, Musallam K, *et al*, Guidelines for the management of non transfusion dependent thalassaemia (NTDT). Nicosia, Cyprus: Thalassaemia International Federation, 2013

²⁵ Cappellini MD, Cohen A, Eleftheriou A, Piga A, Porter J, Taher A, Guidelines for the Clinical Management of Thalassaemia 2nd edition revised, 2008

approximately 40 patients. In addition, growth in this population and the sexual development of children between age greater than or equal to 10 to less than 18 will be assessed. Additional details of this study (which also serves to address post approval commitments in the USA and the EU) will be described in the next Exjade RMP version 9.0 (December 2013). Safety reports for the study are planned at annual intervals.

Although iron accumulation in NTDT is slower than in regularly transfused thalassemia major patients, it is a process that starts at birth in this genetic disease characterised by ineffective erythropoiesis. Iron overload in NTDT children may develop as early as 5 years of age²⁶, with iron related morbidity starting to manifest from 10 years of age²⁷. In Study A2209, mean (range) LIC in paediatric patients at baseline was 9.3 (5.0 to 17.4) mg Fe/g dw with 71.4% of patients having severely elevated LIC greater than 7 mg Fe/g dw. This is the main rationale for deferasirox being indicated for NTDT patients aged 10 years and older.

Effective management of iron overload is especially critical as paediatric patients move into adolescence, when compliance to iron chelation therapy with deferoxamine is known to worsen. The sequelae of iron overload in relation to growth and sexual maturation in thalassemia major patients are well documented. Patterns of growth in these patients are relatively normal until the age of 9 to 10 years when growth velocity begins to slow resulting in stunted pubertal growth spurt and delay or arrest of secondary sexual development.²⁸ As such, beginning chelation therapy before the age of puberty (10 to 11 in girls and 11 to 12 in boys) can help children attain normal sexual maturation.²⁹ With reference again to chelation therapy in transfusional iron overload, the TIF 2008 guidelines²⁸ state that

'therapy started before the age of 10 years reduces the incidence of hypogonadism as well as other endocrine disturbances, including diabetes mellitus',

and that hypothyroidism

'may occur in severely anaemic and/or iron overloaded patients, usually appearing in the second decade of life. The condition is uncommon in optimally treated patients.'

Similarly, data show that several iron related morbidities in NTDT patients start manifesting at 10 years of age.³⁰

Iron overloaded patients with NTDT have a significantly increased risk of hypogonadism³¹. Based on the data in children 2 years and older for the treatment of chronic iron overload due to blood transfusions, data from the pivotal NTDT Study A2209 and its extension, safety in children is adequately studied. The long term safety profile of deferasirox in the treatment of paediatric patients with NTDT will be addressed in the upcoming E 2422 Study. Novartis has also provided compelling reasons for proposing 10 years as an appropriate age cut off for the use of deferasirox in paediatric patients with NTDT.

²⁶ Cossu P, Toccafondi C, Vardeu F, *et al*, Iron overload and desferrioxamine chelation therapy in beta-thalassaemia intermedia. *Eur J Pediatr*; 137: 267-71, 1981

²⁷ Taher AT, Musallam KM, El-Beshlawy A, Age-related complications in treatment naïve patients with thalassaemia intermedia. *Br J Haematol*; 150: 486-9, 2010

²⁸ Cappellini MD, Cohen A, Eleftheriou A, Piga A, Porter J, Taher A, Guidelines for the Clinical Management of Thalassaemia 2nd edition revised, 2008

²⁹ Bronsiegel-Weintrob N, Olivieri NF, Tyler B, Andrews DF, Freedman MH, Holland FJ, Effect of age at the start of iron chelation therapy on gonadal function in beta-thalassaemia major. *N Engl J Med* 323: 713-9, 1990

³⁰ Taher AT, Musallam KM, El-Beshlawy A, Age-related complications in treatment naïve patients with thalassaemia intermedia. *Br J Haematol*; 150: 486-9, 2010

³¹ Musallam KM, Cappellini MD, Wood JC, *et al*, Elevated liver iron concentration is a marker of increased morbidity in patients with beta thalassaemia intermedia. *Haematologica*; 96: 1605-12, 2011

Long term effects

With regard to the comment that

'The proposed starting dose in NTDT is 10 mg/kg/day. This is supported by efficacy outcomes in Study A2209; these outcomes support dose doubling based on assessment of response at week 24. There is some evidence that toxicity is dose dependent (for example, effects on renal function). Without long term follow up, it is difficult to be categorical that long term effects of toxicity at 10 mg/kg/day will be outweighed by the long term benefits of more effective chelation.'

Long term safety in the transfusional iron overlaid setting has been well established over the past decade. With regard to the NTDT setting, Novartis wishes to inform the Delegate that in addition to the completed extension Study 2209E (which supported the use of 20 mg/kg/day), two additional studies are currently being started to confirm the long term safety of the proposed posology:

- Study C1CL670E2419: An open label, multi center, efficacy and safety study of deferasirox in iron overloaded patients (greater than or equal to 10 years of age) with nontransfusion dependent thalassemia. Treatment duration will be up to five years and approximately 117 patients will be enrolled.
- Study C1CL670A2422: An observational, multi center, study to evaluate the long term safety profile of deferasirox in the treatment of chronic iron overload in paediatric patients (age greater than or equal to 10 to less than 18) with non transfusion dependent thalassemia syndromes. Treatment duration will be up to five years and approximately 40 patients will be enrolled.

In summary, the starting dose of 10 mg/kg/day with an optional escalation up to 20 mg/kg/day appears to be the most appropriate dosing regimen in NTDT patients to achieve a clinically meaningful decrease in LIC.

Concluding remark(s)

Novartis welcomes the Delegate's recommendation to approve Exjade deferasirox dispersible tablets *'for the treatment of chronic iron overload in patients with non transfusion dependent thalassemia syndromes ages 10 years and older'*.

With regard to the specific points listed in the Delegate's Overview:

The proposed PI recommendation for starting/stopping rules is in full agreement with the recently issued TIF Guidelines for the Management of NTDT. Flexibility is required to accommodate the mode of clinical monitoring available in Australia. The serum ferritin threshold of 800 µg/L conservatively balances the risk of over chelating patients with low LIC against the risk of missing patients who should be treated.

The safety and efficacy of Exjade in the paediatric patient population has been extensively studied and confirmed for the currently approved indication (chronic transfusional iron overload) for ages 2 and older. The safety data generated in the pivotal Study 2209 support a comparable safety profile across age groups in NTDT; the positive benefit/risk ratio will be confirmed in the additional observational cohort study in paediatric NTDT patients for the age range in which clinically significant iron overload has been observed occur (10 years and older).

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register an extension of indications for a currently registered product.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Exjade dispersible tablets containing 125 mg, 250 mg and 500 mg of deferasirox to have an overall positive benefit-risk profile for the amended 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 committee is requested to provide advice on the following specific issues:

Should the sponsor's starting / stopping rules based on LIC and serum ferritin thresholds be accepted?

The ACPM were of the view that monitoring serum ferritin levels can be problematic, but the guidelines are quite conservative. The proposed starting rule requiring LIC greater than or equal to 5 mg iron/g dry weight or serum ferritin (SF) greater than 800 µg/mL. This differs from the pivotal study where patients required LIC greater than or equal to 5 mg iron/g dry weight and SF greater than or equal to 300 µg/mL. The sponsor provided data to justify this. It seems uncertain whether any NTDT patients would have LIC determined by MRI in Australia. With the recommendation to start treatment when SF greater than 800 µg/L, 91.7% of patients have an LIC greater than or equal to 5 mg iron/g dry weight, and 98.7% of patients have an LIC greater than or equal to 3 mg iron/g dry weight. Conversely, 46.4% of patients will have an LIC greater than or equal to 5 mg iron/g dry weight, but a SF less than 800 µg/L and will be missed for treatment until their SF increases to greater than 800 µg/L. The serum ferritin cut off of 800 µg/L conservatively balances the risk of chelating patients with low LICs (1.3% of patients have LIC less than 3 mg iron/g dry weight) against the risk of missing patients who should be treated.

Should a caveat be added to the indication, noting use of a surrogate endpoint in the pivotal clinical study supporting use in NTDT?

Although efficacy endpoints did not include evaluation of survival, relief of symptoms or end organ damage, liver iron concentration (LIC) correlates with morbidity and the endpoint chosen was reasonable. Morbidity studies in non transfusion dependent thalassemia (NTDT) would take a very long time to conduct.

The ACPM advised the proposed statement that data are based on surrogate endpoints and improvement in survival or disease related symptoms has not been established is not considered necessary. The proposed PI already includes information under Clinical Trials, stating that clinical trials to demonstrate increased survival or to confirm clinical benefit have not been completed. This seems reasonable.

Given the fairly limited exposure in children, should the indication include children 10 years and older?

Although there were few children in Study A2209, outcomes were comparable and it seems reasonable to allow use in children 10 years of age or above.

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Exjade dispersible tablets containing deferasirox, indicated for:

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.

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

Specific conditions of registration applying to these therapeutic goods

The Exjade Risk Management Plan (RMP), version 7.0, dated 8 November 2011, included with submission PM-2012-03063-I-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at less than <http://www.tga.gov.au/hp/information-medicines-pi.htm> greater than.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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