25 April 2013
EMA/CHMP/294499/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Exjade

International non-proprietary name: DEFERASIROX

Procedure No. EMEA/H/C/000670/II/0025

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse event
DFO	Deferoxamine
DFX	Deferasirox
Dw	Dry weight
CrCl	Creatinine clearance
FAS	Full analysis set
Fe	Iron
IE	Iron excretion
LIC	Liver iron concentration
MAH	Marketing Authorisation Holder
MRI	Magnetic resonance imaging
pRBC	packed red blood cells
SAE	Serious adverse event
SAS	Safety analysis set
SD	Standard deviation
SF	Serum ferritin

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd submitted to the European Medicines Agency on 8 December 2011 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Exjade	DEFERASIROX	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH proposed a change of indication for the treatment of infrequently transfused beta-thalassemia major patients in section 4.1. The MAH also proposed to update the product information in line with the latest QRD template (version 8, revision 1).

The variation proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

Exajde was designated as an orphan medicinal product EU/3/02/092 on 13 March 2002.

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/216/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/216/2011 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The MAH did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Pierre Demolis Co-Rapporteur: Luca Pani

Submission date:	8 December 2011
Start of procedure:	18 December 2011
Rapporteur's preliminary assessment report circulated on:	10 February 2012
Co-Rapporteur's preliminary assessment report circulated on:	29 February 2012
Joint Rapporteur's updated assessment report circulated on:	9 March 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	15 March 2012
MAH's responses submitted to the CHMP on:	13 September 2012
Joint Rapporteur's assessment report on the MAH's responses circulated on:	26 October 2012
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	15 November 2012
MAH's responses submitted to the CHMP on:	21 February 2013
Joint Rapporteur's assessment report on the MAH's responses circulated on:	8 April 2013
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	19 April 2013
CHMP opinion:	25 April 2013

2. Scientific discussion

2.1. Introduction

Beta thalassaemia (β-thalassaemia) major syndromes are associated with considerable morbidity and mortality, mostly as a result of iron overload of visceral organs due to repeated blood transfusions. Iron chelation therapy, aimed to remove the excess of iron administered in blood transfusions and to reduce the existing iron burden, represents the mainstay of the treatment of these patients.

Deferoxamine is considered the the comparator reference iron chelation therapy. It is administered by subcutaneous infusion overnight 5 days a week. In consequence, it is associated with poor compliance.

Exjade (deferasirox) is an orally available iron chelator for once daily use. Exjade is indicated for the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older.

Exjade is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups:

- in patients with beta thalassaemia major with iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) aged 2 to 5 years,
- in patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells) aged 2 years and older,
- in patients with other anaemias aged 2 years and older.

In 2012, the indication of Exjade has also been extended for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.

The initial marketing authorisation of Exjade was granted on the basis of Study ICL670C0107. The approved indication was based on the results of a subgroup analysis within this trial. The restriction to use Exjade in infrequently transfused patients when deferoxamine therapy is contraindicated or inadequate resulted from a failure to establish non-inferiority in the subgroup of less severely iron overloaded patients.

In this application, the MAH of Exjade proposed to change the indication by removing this restriction of indication “when deferoxamine therapy is contraindicated or inadequate”, thus proposing the use of deferasirox as first-line treatment in infrequently-transfused patients beta-thalassemia major patients aged 6 years and older. This variation application was supported by an analysis of 2,102 β-thalassemia major patients exposed to deferasirox in 6 completed clinical trials.

Further to the assessment of the CHMP and their conclusions as detailed in this report that this extension of the indication was not considered approvable, the MAH decided not to pursue the proposed change to the indication.

However, the CHMP agreed to the proposal from the MAH to include in section 4.8 of the SmPC a description of the magnitude of the effect on estimated renal clearance based on the retrospective meta-analysis.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application.

2.2.1. Discussion and conclusions on non-clinical aspects

The absence of new non-clinical data was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

- GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

This submission is based on analysis of pooled data from the following six studies:

Study	Study population	Study design	Number of β-thalassemia patients receiving deferasirox treatment
Active comparator studies			
[ICL670A0107] and [ICL670A0107E1]	Patients (≥ 2 years) with β-thalassemia and transfusional haemosiderosis	Multi-center, randomized, open label, parallel-group	Core: 296 Crossover*: 259 Total: 555
[ICL670A0105], [ICL670A0105E1] and [ICL670A0105E2]	Patients (≥ 18 years) with transfusion-dependent iron overload previously treated with DFO.	Multi-center, randomized, open-label, exploratory, parallel-group	Core: 48 Crossover:* 19 Food effect sub-study: 3 Total: 70
Uncontrolled studies			
[ICL670A2402] and [ICL670A2402E1]	β-thalassemia patients (≥ 2 years) with transfusional haemosiderosis who were unable to be satisfactorily treated with DFO or were previously treated with DFP.	Open-label, multi-center, single-arm	Core: 237 of whom 233 entered the extension. Total: 237
[ICL670A2409]	Patients (≥ 2 years) with transfusion-dependent iron overload with or without exposure to prior chelation therapy.	Open-label, multi-center, single-arm	Total: 1115
[ICL670A0108] and [ICL670A0108E1]	Patients (≥ 2 years) with transfusional haemosiderosis unsuitable for treatment with DFO.	Open-label, multi-center, single-arm	Core: 85 of whom 77 entered the extension. Total: 85
[ICL670A0106] and [ICL670A0106E1]	Transfusion-dependent β-thalassemia major patients (≥ 2 to <18 years) previously treated with DFO.	Multi-center, open-label, non-comparative, exploratory phase	Core: 40 of whom 39 entered the extension. Total: 40

*Patients randomized to deferoxamine in the core phase who crossed over to deferasirox in the extension phase
DFO: deferoxamine. DFP: deferiprone.

Given the difference in exposure in these 6 studies, the MAH supported this application with analyses performed separately as follows:

- Study ICL670A2409, consisting of 1,115 β-thalassemia patients who received deferasirox (treatment duration of one year),
- Core Study ICL670A2402 and its extension ICl670A2402E1 (combined treatment duration of up to 3 years), consisting of 237 β-thalassemia patients who received deferasirox,
- Pool database of studies ICL670A0105, ICL670A0106, ICL670A0107, ICL670A0108 and their extensions (treatment duration of up to 5 years), consisting of 750 β-thalassemia patients who received deferasirox.

During the evaluation, the MAH also provided data from a pooled analysis of the six studies ("extended pooled safety set") as well as a retrospective analysis of the data obtained in the

pivotal study A0107 providing comparative results of deferasirox (DFX) versus deferoxamine (DFO) in infrequently transfused patients.

2.4. Clinical efficacy

2.4.1. Main studies

Methods

The table below summarises the study design characteristics of the 6 studies.

Table 1 - Study design characteristics

	Study A0105/E	Study A0106/E	Study A0107/E	Study A0108/E	Study A2402/E	Study A2409
Disease	Transfusion- dependent β-thalassemia	transfusion-dependent β-thalassemia	transfusion-dependent β-thalassemia	transfusion-dependent iron overload	transfusion-dependent β-thalassemia	transfusion-dependent iron overload
Study design	Randomized, parallel-group, active comparator (DFO)	non-comparative	Randomized, parallel-group, active comparator (DFO)	non-comparative	non-comparative	non-comparative
Key objective	Safety	Safety	Efficacy (LIC)	Efficacy (LIC)	Efficacy (LIC)	Efficacy (ferritin)
Key endpoints						
Efficacy	Change in LIC	Treatment success based on LIC	Treatment success based on LIC	Treatment success based on LIC	Treatment success based on LIC	Change in ferritin
Safety	Frequency of AEs and lab abnormalities	Frequency of AEs and lab abnormalities	Frequency of AEs and lab abnormalities	Frequency of AEs and lab abnormalities	Frequency of AEs and lab abnormalities	Frequency of AEs and lab abnormalities
Key inclusion criteria	Age ≥ 18 years LIC 5-15 mg Fe/g dw SF 2000-8000 ng/ml	Age 2-17 years LIC ≥ 2.5 mg Fe/g dw SF ≥ 1000 ng/mL	Age ≥ 2 years LIC ≥ 2 mg Fe/g dw	Age ≥ 2 years LIC ≥ 2 mg Fe/g dw	Age ≥ 2 years LIC ≥ 2 mg Fe/g dw SF >500 ng/ml	Age ≥ 2 years LIC ≥ 2 mg Fe/g dw
Key exclusion criteria	CrCl <80 ml/min	SCr >ULN	SCr >ULN	SCr >ULN	SCr >ULN	SCr >ULN
DFX doses	10 mg/kg or 20 mg/kg daily and dose adjustment within the range 5 – 40 mg/kg titrated according to changes in LIC	10 mg/kg/day with dose adjustment up to 40 mg/kg/day	5-30 mg/kg/day depending on baseline LIC with dose adjustment up to 40 mg/kg/day	5-30 mg/kg/day depending on baseline LIC with dose adjustment up to 40 mg/kg/day	10-20 mg/kg/day with dose adjustment up to 40 mg/kg/day	10-30 mg/kg/day with dose adjustment up to 40 mg/kg/day
Demographics (all underlying conditions)						
Age (years)						
Mean (SD)	24.0 (5.0)	10.4 (4.37)	17.7 (9.64)	24.7 (10.03)	13.0 (6.93%)	18.2 (10.86)
Median (range)	24.0 (17.0-50.0)	11.5 (2.0-17.0)	16.0 (2.0-54.0)	23.0 (4.0-59.0)	12.0 (2.0-42.0)	17.0 (2.0-72)
Sex, n (%)						
Male	26 (36.6%)	17 (42.5%)	274 (49.4%)	42 (49.4%)	117 (50.6%)	538 (48.3)
Female	45 (63.4%)	23 (57.5%)	281 (50.6%)	43 (50.6%)	114 (49.4%)	577 (51.7)

Study participants

Study ICL670A0105: patients (≥ 18 years) with transfusion-dependent iron overload (Liver iron concentration (LIC): ≥ 5 to ≤ 15 mg Fe/g dw) previously treated with deferoxamine.

Study ICL670A0107: β-thalassemia patients (≥ 2 years) with transfusional haemosiderosis (LIC: ≥ 2 mg Fe/g dw, transfusions ≥ 8 per year).

Study ICL670A0106: paediatric patients (≥ 2 to ≤ 17 years) with transfusion dependent β-thalassaemia major (LIC: ≥ 2.5 mg Fe/g dw or SF ≥ 1000 µg/L) previously treated with deferoxamine (for ≥ 4 weeks).

Study ICL670A0108: Patients (≥ 2 years) with chronic anaemias and transfusional haemosiderosis unsuitable for treatment with deferoxamine. In this analysis only patients with transfusional haemosiderosis due to β-thalassemia were included.

- Patients with β-thalassemia and documented non-compliance to deferoxamine were defined as having taken < 50% of the prescribed doses in the 12 months prior to study entry, with LIC ≥ 14 mg Fe/g dw.
- Patients with β-thalassaemia inadequately chelated with deferoxamine due to contraindications and/or due to documented unacceptable toxicity of deferoxamine, or

documented poor response to deferoxamine despite proper compliance, with LIC ≥ 2 mg Fe/g dw.

Study ICL670A2402: patients (≥ 2 years) with transfusional haemosiderosis who were previously treated with deferiprone or deferoxamine. The patients in the study were:

- β-thalassaemia outpatients with transfusional haemosiderosis and unable to be chelated with deferoxamine due to deferoxamine being contra-indicated and/or due to documented unacceptable toxicity of deferoxamine or documented poor response to deferoxamine despite proper compliance, with SF ≥ 500 µg/L and LIC ≥ 2 mg/Fe/g dw liver.
- β-thalassaemia outpatients with transfusional haemosiderosis and documented noncompliance to deferoxamine, defined as having taken less than 50% of the prescribed chelation therapy doses in the 12 months prior to study entry
- β-thalassemia outpatients with transfusional haemosiderosis treated with deferiprone, who discontinued deferiprone treatment at least 28 days before Day 1 of this study, and had SF ≥ 500 µg/L and LIC ≥ 2 mg/Fe/g dw.

Study ICL670A2409: patients (≥ 2 years) with transfusion-dependent iron overload who had been previously treated with chelation therapy as well as patients who had not. The patients presented with iron overload as shown by SF ≥ 1000 µg/L at start of study or patients presenting with SF <1000 µg/L but with history of multiple transfusions (> 20 transfusions or 100 mL/kg of packed red blood cells [pRBC]) and LIC >2 mg Fe/g dw (as confirmed by R2-MRI).

Treatments

- Controlled studies

Study ICL670A0105: randomisation 1:1:1 to oral deferasirox 10mg/kg/day, oral deferasirox 20mg/kg/day or subcutaneous infusions of deferoxamine 20 mg/kg/day for 5 consecutive days a week. Subsequent dose-titrations were based on change in LIC, determined every 3 months by a non-invasive method (SQUID) over 12 months.

Intermediate extension phase (ICL670A0105E1): after completing 12 months of treatment consenting patients who were considered to be deriving benefit from treatment, continued to receive study therapy

Non comparative long term extension (ICL670A0105E2): patients who completed the intermediate extension phase were eligible to receive deferasirox treatment for 5 years.

Study ICL670A0107: Patients were randomised (1:1) to once-daily oral doses of deferasirox 5 to 40 mg/kg/day for 7 days/week or subcutaneous infusions of deferoxamine 20 to 60 mg/kg/day for 5 consecutive days/week. After randomisation to deferasirox or deferoxamine patients were assigned to different dose cohorts (5, 10, 20 or 30 mg/kg) by the Investigator according to their baseline LIC values, with doses fixed during the first year and subsequent dose titration based on safety and efficacy.

Extension study (ICL670A0107E1) enrolled patients who had completed the core study, and was designed primarily to evaluate the long term efficacy and safety of deferasirox in β- thalassemia patients with transfusional haemosiderosis treated for 4 years. In the extension study, all patients received treatment with deferasirox, regardless of their treatment assignment in the core study.

- Uncontrolled studies

Study ICL670A0106: patients were treated with repeated doses of deferasirox 10 mg/kg/day with subsequent dose titration based on change in LIC. SQUID was performed 4 weeks after start of treatment, and then every 12 weeks up to 48 weeks.

Patients who had completed 1-year of study treatment and scheduled assessments in the core study were enrolled into the extension phase ICL670A0106E1, to evaluate the long term safety of deferasirox in paediatric patients with β-thalassemia treated for 5 years

Study ICL670A0108: Once daily oral doses of deferasirox between 5 to 40 mg/kg based on their baseline LIC for one year and subsequent dose-titration was based on safety and efficacy. Patients with LIC of 2 to 3 mg Fe/g dw received deferasirox 5 mg/kg, with LIC of > 3 to 7 mg Fe/g dw received 10 mg/kg, with LIC of > 7 to 14 mg Fe/g dw received 20 mg/kg, and with LIC of > 14 mg Fe/g dw received 30 mg/kg.

Patients who completed at least one year of treatment in the core phase were enrolled in to the 4-year extension phase (ICL670A0108E), to evaluate the long term safety and tolerability profile of deferasirox.

Study ICL670A2402: Fixed starting once-daily dose of 10 or 20 mg/kg/day based on baseline LIC, with subsequent dose adjustments based on SF levels.

Patients who completed at least one year of treatment in the core phase were enrolled into the 2-year extension phase (ICL670A2402E1), to evaluate the long term safety and tolerability profile of deferasirox.

Study ICL670A2409: initial recommended daily dose of deferasirox was 20 mg/kg/day body weight for patients who had received blood transfusions with a frequency of about 2 to 4 units/month of pRBC (7to 14 mL pRBCs/kg/month). An initial daily dose of 30 mg/kg/day was considered for patients receiving more frequent blood transfusions and 10 mg/kg/day for patients receiving less frequent transfusions or for patients receiving exchange transfusions. Subsequent doses were titrated based on the combined evaluation of efficacy and safety parameters.

Objectives

Key objectives are described in Table 1.

Outcomes/endpoints

Key endpoints are described in Table 1. Blood intake was expressed as pRBC volume per kilogram body weight per month (mL/kg/month) and the blood intake groups (blood intake derived from one year of treatment) were categorised following the definition used in the current SPC for deferasirox:

- Infrequently transfused patients: < 7 mL pRBCs/kg/month
- Frequently transfused patients: 7 to 14 and > 14 mL pRBCs/kg/month
- The formula used to calculate the average blood intake in mL/kg/month was: (total sum of blood transfused by weight) / (corrected transfusion exposure / month), where:
- Total sum of blood transfused by weight (mL/kg) is the sum of [(amount of blood transfused [mL]) × haematocrit (%) / 100] / (body weight (kg) at transfusion). If the transfusion record's haematocrit value was missing, it was imputed by the haematocrit value provided by the respective centre. If the amount of blood transfused was not

expressed in mL (or cm3), it was first converted to mL. For units expressed in 'pack', 'unit' or 'bag', it was assumed that one pack/unit/bag was 200 mg iron, i.e. 185 mL of RBC.

- Corrected transfusion exposure was the normal exposure plus a correction factor, i.e. (last transfusion date − first transfusion date + 1) + ([last transfusion date − first transfusion date + 1] / [number of transfusion records − 1]).

The efficacy of deferasirox was also assessed by groups of age at first dose (2 to <6, 6 to <12, 12 to <18, and ≥ 18 years) and average dose (<7.5, 7.5 to 12.5, >12.5 to 17.5, >17.5 to <25, 25 to <35, and ≥ 35 mg/kg/day). These dose groups correspond to deferasirox doses used in clinical practice (5, 10, 15, 20, 30 and 40 mg/kg/day, respectively).

The efficacy characterization was based on changes after 1 year of treatment with deferasirox in:

- Serum Ferritin (SF)
- Liver Iron Concentration (LIC)
- Iron Excretion (IE)

In addition, long term efficacy, up to 5 years of treatment, was assessed. In order to account for the exposure differences across the 3 datasets, data were provided by yearly periods of treatment (a year was defined as 365 days).

Sample size

Not applicable.

Randomisation

In studies ICL670A0105 and ICL670A0105, patients were randomised to oral deferasirox or subcutaneous infusion of deferoxamine. ICL670A0105 was a three arm study, as two doses of deferasirox (10 or 20 mg/kg/day) were tested, while in ICL670A0107 a range of dose (5-40 mg/kg/day) was allowed in the deferasirox arm.

Blinding (masking)

Not applicable.

Statistical methods

The efficacy parameters were analysed using the following analysis sets:

- Safety Analysis Set (SAS) comprised all patients who received at least one dose of deferasirox and had at least one post-baseline safety assessment.
- Full Analysis Set (FAS) comprised all patients who successfully passed screening and had been selected to start study medication in the context of the respective protocol.

The FAS, which required that patients be randomised or assigned to a treatment, but not necessarily treated, was used for studies ICL670A2409 and ICL670A2402. For the Pool, the SAS was used; this database had been previously created to perform safety analysis of deferasirox and all patients included were treated with deferasirox. Thus, efficacy and safety analyses in this report are based on the SAS for the Pool dataset.

Results

Baseline data

Demographics and baseline characteristics of the overall population are summarised in Table 2.

Table 2 - Demographics and other baseline characteristics (SAS)

	Study 2409 N=1115	Pool N=750	Study 2402 N=237
Age (years)			
Mean (SD)	18.2 (10.89)	18.7 (9.77)	13.4 (7.08)
Median	17.0	18.0	12.0
Range	2.0, 72.0	2.0, 59.0	2.0, 42.0
Age category (years), n (%)			
< 6	130 (11.7)	56 (7.5)	27 (11.4)
6 to < 12	215 (19.3)	143 (19.1)	76 (32.1)
12 to < 18	253 (22.7)	172 (22.9)	79 (33.3)
≥ 18	517 (46.4)	379 (50.5)	55 (23.2)
Sex, n (%)			
Male	538 (48.3)	358 (47.7)	120 (50.6)
Female	577 (51.7)	392 (52.3)	117 (49.4)
Race, n (%)			
Caucasian	468 (42.0)	654 (87.2)	70 (29.5)
Black	2 (0.2)	3 (0.4)	0
Asian	594 (53.3)	30 (4.0)	125 (52.7)
Other	51 (4.6)	63 (8.4)	42 (17.7)
n^	1104	747	236
Mean (SD) (3309.13)	4036.1 (2928.59)	2697.5 (1963.65)	4228.4
Median	3159.0	2127.0	3384.5
Range	462.0, 25184.0	252.0, 15050.0	744.0, 32068.0
SF category (µg/L), n (%)			
≤ 1000	26 (2.3)	79 (10.5)	3 (1.3)
> 1000 to 2500	366 (32.8)	375 (50.0)	68 (28.7)
> 2500	712 (63.9)	293 (39.1)	165 (69.6)
Missing	11 (1.0)	3 (0.4)	1 (0.4)
LIC (mg Fe/g dw)			
n^	286*	749	237
Mean (SD)	22.7 (12.87)	12.4 (9.20)	18.7 (9.89)
Median	24.0	9.5	17.5
Range	1.6, 54.8	0.8, 56.3	2.1, 48.9
LIC category (mg Fe/g dw), n (%)			
< 5	25 (2.2)	137 (18.3)	11 (4.6)
5 to 7	26 (2.3)	122 (16.3)	13 (5.5)
> 7 to 15	46 (4.1)	277 (36.9)	72 (30.4)
> 15	189 (17.0)	213 (28.4)	141 (59.5)
Missing	829 (74.3)*	1 (0.1)	0

SF = Serum ferritin; LIC = Liver iron concentration.
*LIC was assessed only in a subgroup of patients as a secondary objective.
^Patients with available SF and LIC assessments. Age is age in years at first dose.

Numbers analysed

Table 3 - Analysis sets by blood intake categories

	Study 2409* n (%)	Pool* n (%)	Study 2402* n (%)	All studies n (%)
All patients	1115 (53.0)	750 (35.7)	237 (11.3)	2102 (100.0)
<7 mL pRBCs/kg/month	195 (17.5)	65 (8.7)	47 (19.8)	307 (14.6)
7 to 14 mL pRBCs/kg/month	701 (62.9)	567 (75.6)	165 (69.6)	1433 (68.2)
>14 mL pRBCs/kg/month	187 (16.8)	114 (15.2)	24 (10.1)	325 (15.5)
Missing	32 (2.9)	4 (0.5)	1 (0.4)	37 (1.8)

* For studies 2409 and 2402, SAS was used to analyze patient disposition, baseline characteristics, exposure and safety analyses, while FAS was used to analyze the efficacy endpoints. For Pool dataset SAS was used for all analyses. FAS = Full analysis set; SAS= Safety analysis set.

Outcomes and estimation

Results for serum ferritin changes at the end of one year of treatment and in the subsequent years are shown in Tables 4 and 5. Results of serum ferritin changes from the pooled analysis of the six studies ("extended pooled safety set") are shown in Figures 1-2. Liver Iron Concentration changes are shown in Tables 6-7 and Figures 3-4. Iron excretion values are summarised in Tables 8-9.

- Serum Ferritin changes

Table 4 - Mean change in serum ferritin (µg/L) by blood intake categories in the first year of treatment*

Blood intake categories#	Study 2409 N=1115		Pool Y1 N=750		Study 2402 Y1 N=237	
	n^	Mean change (95% CI)	n^	Mean change (95% CI)	n^	Mean change (95% CI)
All patients	**1086**	**-258.9 (-371.9, -145.9)**	**743**	**100.3 (6.8, 193.7)**	**237**	**-447.4 (-633.0, -231.8)**
< 7 mL/kg/month	194	-933.5 (-1217.9, -649.2)	65	-543.2 (-932.6, -153.9)	47	-640.9 (-966.6,-315.2)
7-14 mL/kg/month	691	-118.8 (-259.2, 21.5)	564	104.6 (-2.6, 211.8)	165	-462.5 (-749.0, -176.0)
> 14 mL/kg/month	186	-38.8 (-290.0, 212.4)	113	450.4 (270.9, 630.0)	24	-24.3 (-549.1, 500.5)
Missing	15	-717.3 (-1420.4, -14.2)	1	-78.0	1	986.0

*Analysis sets: Studies 2409 and 2402 = FAS, Pool = SAS.
^Patients with available serum ferritin assessments.
#Blood intake categories in Year 1.

Table 5 - Mean change in serum ferritin (µg/L) by blood intake during years 2 to 5 of treatment*

Blood intake categories[#] (mL/kg/month)	Pool Y2 N=682		Pool Y3 N=609		Pool Y4 N=551		Pool Y5 N=315		Study 2402 Y2 N=231		Study 2402 Y3 N=217	
	n[^]	Mean change[§] (95% CI)	n[^]	Mean change[§] (95% CI)	n[^]	Mean change[§] (95% CI)	n[^]	Mean change[§] (95% CI)	n[^]	Mean change[§] (95% CI)	n[^]	Mean change[§] (95% CI)
All patients	674	**-3.1 (-86.1, 79.9)**	**595**	**-211.7 (-284.4, -139.1)**	**478**	**-141.4 (-217.1, -65.7)**	**250**	**-152.5 (-251.2, -53.7)**	**231**	**-751.8 (-920.5, -583.2)**	**215**	**-272.8 (-428.6, -117.0)**
< 7	73	-135.4 (-366.6, 95.8)	75	-259.7 (-502.4, -17.1)	77	-24.5 (-248.2, 199.2)	44	-316.5 (-591.2, -41.7)	61	-931.8 (-1265.4, -598.2)	48	-231.5 (-541.7, 78.7)
7-14	518	14.8 (-83.9, 113.5)	452	-190.6 (-273.5, -107.7)	342	-152.3 (-239.3, -65.3)	182	-99.1 (-211.2, 12.9)	159	-667.7 (-868.2, -467.3)	149	-292.8 (-494.5, -91.1)
> 14	77	14.3 (-190.6, 219.3)	68	-299.0 (-480.0, -118.1)	59	-231.0 (-433.6, -28.4)	23	-252.9 (-587.8, 82.1)	11	-969.7 (-2035.8, 96.3)	11	-469.1 (-1076.1, 137.8)
Missing	6	-157.8 (-321.5, 5.8)	0	0	0	0	1	-337.0	0	0	12	-56.2 (-207.3, 94.9)

*Analysis sets: Study 2402 = FAS, Pool Y = SAS.
[^]Patients with available serum ferritin assessments.
[§]Mean change from the previous year.
[#]Blood intake categories in Years 2 to 5.

Figure 1 – Mean change in SF by blood intake and average dose in Year 1 (Extended Pooled Safety Set)

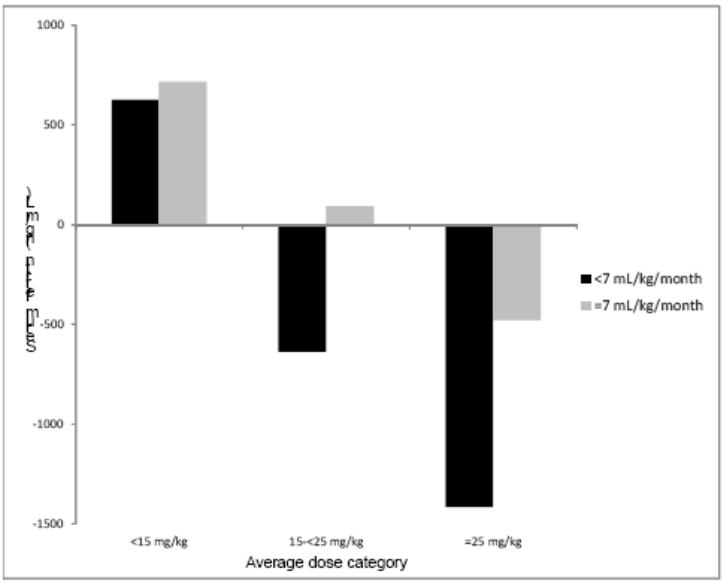
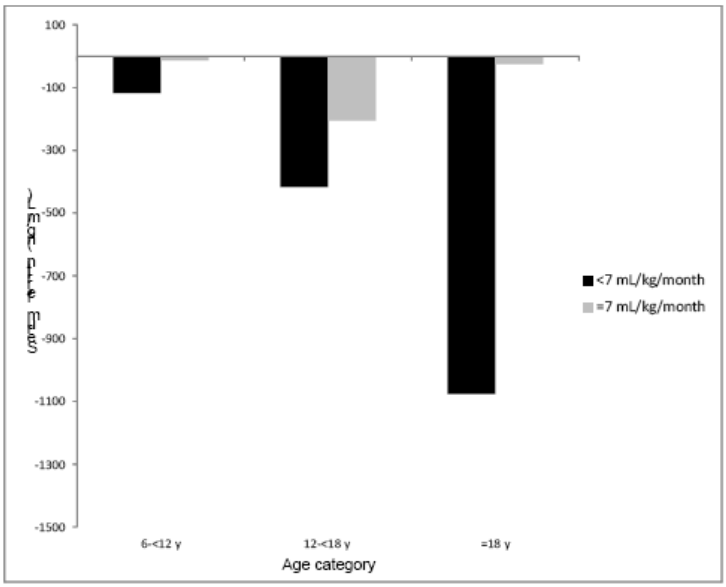


Figure 2 – Mean change in SF by blood intake and age in Year 1 (Extended Pooled Safety Set)



Children <6 years not presented due to low number of infrequently transfused patients (n=2)

- Liver Iron Concentration changes

Table 6 - Mean change in liver iron concentration (mg Fe/g dw) by blood intake categories in the first year of treatment*

Blood intake categories[#]	Study 2409 N=1115		Pool Y1 N=750		Study 2402 Y1 N=237	
	n[^]	Mean change (95% CI)	n[^]	Mean change (95% CI)	n[^]	Mean change (95% CI)
All	**271**	**-4.2 (-5.1, -3.2)**	**349**	**-1.7 (-2.5, -1.0)**	**148**	**-1.8 (-2.9, -0.6)**
< 7 mL/kg/month	71	-5.1 (-7.4, -2.8)	28	-4.4 (-7.5, -1.3)	28	-1.0 (-3.9, 1.8)
7-14 mL/kg/month	167	-4.0 (-5.2, -2.8)	264	-2.1 (-2.9, -1.2)	102	-2.7 (-4.0, -1.3)
> 14 mL/kg/month	31	-3.1 (-6.0, -0.2)	57	1.2 (-0.6, 3.0)	18	2.2 (-0.9, 5.3)
Missing	2	-0.9 (-27.6, 25.8)	0	0	0	0

*Analysis sets: Studies 2409 and 2402 = FAS, Pool Y = SAS.
[^]Patients with available liver iron concentration assessments.
[#]Blood intake categories in Year 1.

Table 7 - Mean change in liver iron concentration (mg Fe/g dw) by blood intake categories during years 2 to 5 of treatment*

Blood intake categories[#]	Pool Y2-5[&] N=682		Study 2402 Y2 N=231		Study 2402 Y3 N=217	
	n[^]	Mean change[§] (95% CI)	n[^]	Mean change[§] (95% CI)	n[^]	Mean change[§] (95% CI)
All	**166**	**-0.7 (-1.7, 0.2)**	**137**	**-2.3 (-3.4, -1.1)**	**157**	**-3.4 (-4.3, -2.4)**
< 7 mL/kg/month	11	-0.4 (-4.7, 3.8)	36	-4.1 (-6.4, -1.9)	39	-3.9 (-6.0, -1.9)
7-14 mL/kg/month	136	-0.3 (-1.3, 0.8)	95	-1.5 (-2.9, -0.2)	108	-3.1 (-4.2, -2.0)
>14 mL/kg/month	19	-4.0 (-6.7, -1.3)	6	-3.0 (-8.0, 1.9)	4	-6.3 (-15.4, 2.8)
Missing	0	0	0	0	6	-2.5 (-10.5, 5.4)

*Analysis sets: Study 2402 = FAS, Pool Y2-5 = SAS.
[&]In the pool dataset year-wise representation is not available as LIC was only measured at end of the study for the pooled extension studies (years 2 to 5).
[^]Patients with available liver iron concentration assessments.
[§]Mean change from previous year.
[#]Blood intake categories in Years 2 to 5.

Figure 3 – Mean change in LIC by blood intake and average dose in Year 1 (Extended Pooled Safety Set)

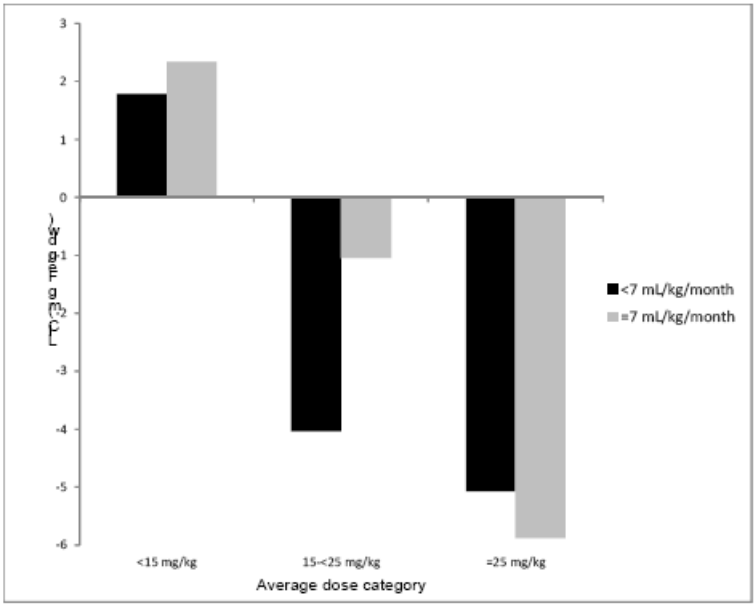
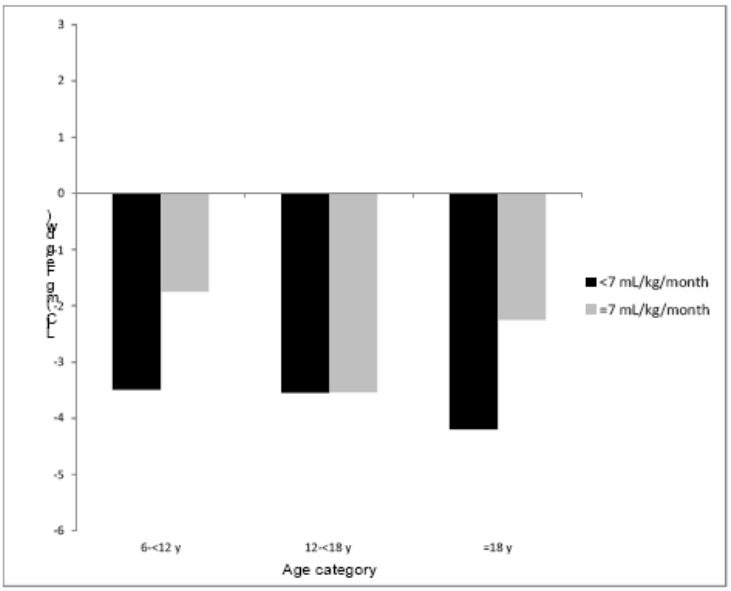


Figure 4 – Mean change in LIC by blood intake and age in Year 1 (Extended Pooled Safety Set)



Children <6 years not presented as there were no infrequently transfused patients with LIC assessment.

- Iron Excretion

Table 8 - Iron excretion (mg/kg/day) by blood intake categories in the first year of treatment*

Blood intake categories[#]	Study 2409 Y1 N=1115		Pool Y1 N=750		Study 2402 Y1 N=237	
	n[^]	Absolute value (95% CI)	n[^]	Absolute value (95% CI)	n[^]	Absolute value (95% CI)
All	**269**	**0.4 (0.4, 0.5)**	**349**	**0.4 (0.4, 0.4)**	**148**	**0.4 (0.3, 0.4)**
< 7 mL/kg/month	71	0.3 (0.2, 0.4)	28	0.3 (0.2, 0.4)	28	0.2 (0.1, 0.3)
7-14 mL/kg/month	167	0.5 (0.4, 0.5)	264	0.4 (0.4, 0.4)	102	0.4 (0.3, 0.4
>14 mL/kg/month	31	0.7 (0.5, 0.8)	57	0.5 (0.4, 0.5)	18	0.4 (0.3, 0.5)

*Analysis sets: Studies 2409 and 2402 = FAS, Pool Y = SAS.
[^]Patients with available iron assessments
[#]Blood intake categories in Year 1.

Table 9 - Iron excretion (mg/kg/day) by blood intake categories during years 2 to 5 of treatment*

Blood intake categories[#]	Pool Y2-5[&] N=682		Study 2402 Y2 N=231		Study 2402 Y3 N=217	
	n[^]	Absolute value (95% CI)	n[^]	Absolute value (95% CI)	n[^]	Absolute value (95% CI)
All	**165**	**0.4 (0.4, 0.4)**	**137**	**0.4 (0.3, 0.4)**	**151**	**0.5 (0.4, 0.6)**
<7 mL/kg/month	11	0.2 (0.2, 0.3)	36	0.3 (0.2, 0.4)	39	0.5 (0.3, 0.6)
7-14 mL/kg/month	135	0.4 (0.4, 0.4)	95	0.4 (0.3, 0.4)	108	0.5 (0.4, 0.6)
>14 mL/kg/month	19	0.5 (0.5, 0.6)	6	0.6 (0.5, 0.7)	4	0.8 (0, 1.6)

*Analysis sets: Study 2402 = FAS, Pool Y = SAS.
[&]In the pool dataset year-wise representation is not available as iron excretion rates were derived only at end of the study for the pooled extension studies (years 2 to 5).
[^]Patients with available iron assessments
[#]Blood intake categories in years 2 to 5.

Ancillary analyses

Comparisons of efficacy and safety between DFX and DFO by blood intake categories were performed within study A0107. In this study, infrequently transfused patients were comparable to frequently transfused patients in terms of age and race. The proportion of female patients and the baseline SF values tended to be higher in infrequently transfused patients. Results are summarised in Table 10 and Figures 5-6.

Table 10 – Number of patients by average dose group and blood intake and treatment group (A0107 Safety Set)

	Blood intake <7 mL/kg/month		Blood intake ≥ 7 mL/kg/month	
	DFX N=24	DFO N=18	DFX N=272	DFO N=272
Average daily dose category	%	%	%	%
DFX <15 / DFO<30 mg/kg/day	33.3	5.6	34.2	6.3
DFX 15 to <25 / DFO 30 to <50 mg/kg/day	29.2	66.7	32.7	64.7
DFX ≥ 25 / DFO ≥ 50 mg/kg/day	37.5	27.8	33.1	29.0

Figure 5 – Mean change in SF by blood intake and average deferasirox and deferoxamine dose (A0107 PP-1)

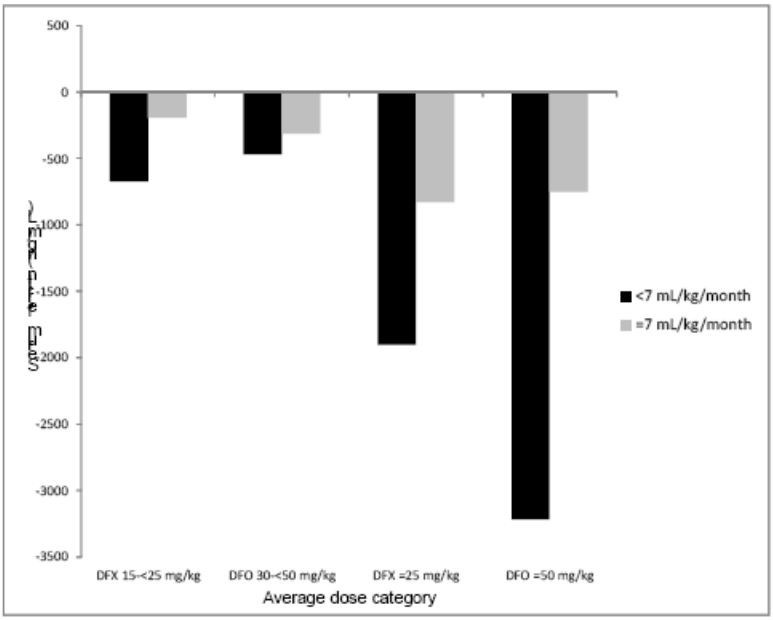
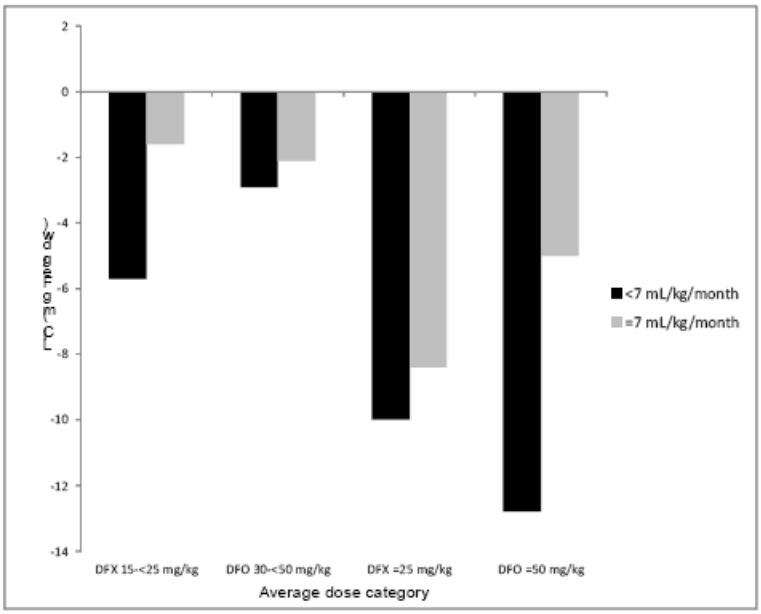


Figure 6 – Mean change in LIC by blood intake and average deferasirox and deferoxamine dose (A0107 PP-1)



Patients from lowest dose categories are not presented due to only one deferoxamine-treated patient)

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The aim of this application was to demonstrate efficacy (and safety) of deferasirox in infrequently transfused beta-thalassemia patients in first line therapy. To do so, the MAH did not conduct a new randomised study to compare deferasirox with the standard of care deferoxamine in the infrequently-

transfused population. The MAH supported this objective by comparing the activity of deferasirox between infrequently-transfused and frequently-transfused patients.

The MAH presented a descriptive analysis of pooled individual data from 6 deferasirox studies (phase II to phase IV) without an active comparator. This descriptive analysis was performed by subgroup.

Studies were heterogeneous, especially in terms of intervention and consequently results were presented separately in 3 main datasets. However, presentation in three separate datasets in order to account for the heterogeneity was considered insufficient.

Specification of starting dose based on transfusion requirements was implemented only after the first studies. Furthermore, schedule of dose titration was different across studies, whereby deferasirox dose was maintained constant for the first year of treatment in some studies, whereas in other studies dose-titration was possible, based on efficacy markers. Additionally, dose titration (during the first year of treatment and after) was not standardised across the trials. These discrepancies may affect the comparability of the intervention among the samples and consequently affect robustness of efficacy conclusions that might be drawn from the datasets.

The additional pooled analysis of the six studies provided by the MAH presented several major methodological weaknesses which impacted the reliability of its results (clinical heterogeneity of the studies, retrospective categorisation of the patients with potential biases in this allocation and potential non comparability of the groups).

Similarly, the retrospective analysis of the data obtained in the pivotal study A 0107 presented several major methodological weaknesses (retrospective allocation of the patients in subgroups, no statistical testing strategy, small sample size of the subgroups especially for infrequently transfused patients) and therefore cannot be considered as a reliable comparison of the efficacy of DFX versus DFO.

Contradictory results were observed in the different datasets, which could be related to the different criteria to modify the dose (LIC or serum ferritin variations) in each single study and further underlines the heterogeneity of the examined trials and the difficulty to draw any incontrovertible conclusion of efficacy. Consequently, the Pool overall change is hardly interpretable.

2.4.3. Conclusions on the clinical efficacy

The submitted analyses do not provide sufficient level of evidence to establish that the clinical efficacy of deferasirox in infrequently transfused patients with β-thalassemia major is non-inferior to deferoxamine.

Further to the assessment of the CHMP and their conclusions as detailed in this report that this extension of the indication was not considered approvable, the MAH decided not to pursue with the proposed change to the indication.

2.5. Clinical safety

The safety evaluation was based on analysis of 2,102 β-thalassaemia major patients exposed to deferasirox (mean daily dose 22.4-25.7 mg/kg/day) in 6 completed trials. Five of these studies consisted of a core phase and an extension phase (with treatment durations of up to 5 years) aimed to assess long term safety. Two of these studies involved the use of the active comparator deferoxamine as a control. This analysis allowed a quantitative characterisation of the safety of deferasirox in patients with infrequent blood transfusions (<7 mL pRBCs/kg/month) in comparison with frequently transfused patients (≥ 7 mL pRBCs/kg/month).

The safety population comprised all patients from the 6 clinical studies who received at least one dose of study drug and had at least one post-baseline safety assessment.

Due to the differences in exposure in the 6 studies included in this analysis, the studies were grouped into 3 datasets:

- Study ICL670A2409 (treatment duration of one year)
- Pooled database consisting of studies ICL670A0105, ICL670A0106, ICL670A0107, ICL670A0108 and their extensions (treatment duration up to 5 years)
- Study ICL670A2402/E consisting of the core study and its extension ICl670A2402E (treatment duration up to 3 years)

Since the key objective of the safety analysis was to compare the safety of deferasirox by blood intake, patients were categorised into 3 blood intake groups as follows:

- Infrequently transfused patients: <7 mL pRBCs/kg/month
- Frequently transfused patients: 7-14 mL pRBCs/kg/month and >14 mL pRBCs/kg/month

The safety of deferasirox was also assessed by age at first dose and dose.

Patient exposure

This analysis includes exposure of 4,326 patient-years (528 patient-years of exposure for infrequently transfused patients and 3,785 patient-years of exposure for patients receiving more frequent transfusions) including 2,433 patients-years of exposure in paediatric patients.

	Study 2409 N=1115	Pool N=750	Study 2402 N=237
Total patient years	1057	2675	594
Patient years by blood intake			
<7 mL pRBCs/kg/month	192	228	108
7 to 14 mL pRBCs/kg/month	675	2045	420
>14 mL pRBCs/kg/month	177	403	65
Patient years by age range			
<6 years	125	203	73
6 to <12 years	208	545	198
12 to <18 years	248	635	198
≥ 18 years	476	1292	125

Source: [SCS–Table 1-4], [SCS–Table 1-5]

Globally, patients in Study ICL670A2402 were younger compared to patients in Study ICL670A2409 and in the Pool (median age of 12, 17 and 18 years, respectively). Overall, approximately 45% of the patients were ≥ 18 years old (adults), 24% were 12 to <18 years old (adolescents), 20% were 6 to <12 years old (older children), and 10% were <6 years old (young children).

Across the 3 datasets, patients in the low blood intake category were older (median age: 21, 22, and 20 years in Study ICL670A2409, the Pool, and Study ICL670A2402, respectively) compared to patients with moderate (median age: 15, 18, and 12 years, respectively) and high blood intake (median age: 15, 11, and 8 years, respectively).

Adverse events (AE)

Table 11 – Incidence of AE categories by blood intake in the first year of treatment (Safety analysis population)

Preferred term	2409 Y1				Pool Y1				2402 Y1			
Blood intake (mL pRBCs/kg/month)	<7	7-14	>14	All	<7	7-14	>14	All	<7	7-14	>14	All
	n=195	n=701	n=187	N=1115	n=65	n=567	n=114	N=750	n=47	n=165	n=24	N=237
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Overall AEs	137 (70.3)	555 (79.2)	161 (86.1)	880 (78.9)	56 (86.2)	522 (92.1)	87 (76.3)	668 (89.1)	38(80.9)	123 (74.5)	19 (79.2)	181 (76.4)
Severe AEs	13 (6.7)	66 (9.4)	19 (10.2)	105 (9.4)	13 (20.0)	53 (9.3)	2 (1.8)	69 (9.2)	9 (19.1)	8 (4.8)	1 (4.2)	18 (7.6)
Drug-related AEs	68 (34.9)	308 (43.9)	88 (47.1)	487 (43.7)	30 (46.2)	210 (37.0)	31 (27.2)	273 (36.4)	23 (48.9)	70 (42.4)	11 (45.8)	105 (44.3)
SAEs	17 (8.7)	60 (8.6)	15 (8.0)	97 (8.7)	10 (15.4)	50 (8.8)	6 (5.3)	67 (8.9)	7 (14.9)	8 (4.8)	2 (8.3)	17 (7.2)
AEs leading to discontinuation	2 (1.0)	19 (2.7)	9 (4.8)	44 (3.9)	2 (3.1)	15 (2.6)	1 (0.9)	21 (2.8)	0	2 (1.2)	0	2 (0.8)

- AEs in the first year of treatment

Table 12 –AEs regardless of study drug relationship by blood intake and SOC in the first year of treatment (SAS)

System organ class	Study 2409				Pool Y1				Study 2402/E Y1			
Blood intake (mL/kg/month)	<7	7-14	>14	All	<7	7-14	>14	All	<7	7-14	>14	All
	n=195	n=701	n=187	N=1115	n=65	n=567	n=114	N=750	n=47	n=165	n=24	N=237
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any primary SOC	137 (70.3)	555 (79.2)	161 (86.1)	880 (78.9)	56 (86.2)	522 (92.1)	87 (76.3)	668 (89.1)	38 (80.9)	123 (74.5)	19 (79.2)	181 (76.4)
Infections and infestations	80 (41.0)	300 (42.8)	86 (46.0)	470 (42.2)	37 (56.9)	380 (67.0)	67 (58.8)	484 (64.5)	24 (51.1)	63 (38.2)	10 (41.7)	97 (40.9)
Gastrointestinal disorders	48 (24.6)	207 (29.5)	75 (40.1)	341 (30.6)	37 (56.9)	283 (49.9)	39 (34.2)	359 (47.9)	13 (27.7)	47 (28.5)	5 (20.8)	66 (27.8)
General disorders and admin. site conditions	27 (13.8)	143 (20.4)	28 (15.0)	210 (18.8)	22 (33.8)	202 (35.6)	36 (31.6)	260 (34.7)	4 (8.5)	8 (4.8)	4 (16.7)	16 (6.8)
Respiratory, thoracic and mediastinal disorders	22 (11.3)	115 (16.4)	33 (17.6)	171 (15.3)	23 (35.4)	202 (35.6)	20 (17.5)	245 (32.7)	3 (6.4)	12 (7.3)	0	15 (6.3)
Musculoskeletal and connective tissue disorders	26 (13.3)	93 (13.3)	24 (12.8)	144 (12.9)	20 (30.8)	153 (27.0)	12 (10.5)	185 (24.7)	7 (14.9)	8 (4.8)	2 (8.3)	17 (7.2)
Nervous system disorders	24 (12.3)	71 (10.1)	23 (12.3)	119 (10.7)	17 (26.2)	142 (25.0)	17 (14.9)	176 (23.5)	6 (12.8)	8 (4.8)	0	15 (6.3)
Skin and subcutaneous tissue disorders	33 (16.9)	148 (21.1)	71 (38.0)	270 (24.2)	18 (27.7)	118 (20.8)	26 (22.8)	164 (21.9)	5 (10.6)	30 (18.2)	4 (16.7)	39 (16.5)
Investigations	38 (19.5)	188 (26.8)	25 (13.4)	254 (22.8)	18 (27.7)	117 (20.6)	13 (11.4)	148 (19.7)	8 (17.0)	24 (14.5)	2 (8.3)	34 (14.3)
Injury, poisoning and procedural complications	16 (8.2)	46 (6.6)	20 (10.7)	83 (7.4)	13 (20.0)	86 (15.2)	14 (12.3)	114 (15.2)	0	4 (2.4)	2 (8.3)	6 (2.5)
Eye disorders	4 (2.1)	28 (4.0)	12 (6.4)	44 (3.9)	8 (12.3)	45 (7.9)	7 (6.1)	60 (8.0)	1 (2.1)	0	1 (4.2)	2 (0.8)
Ear and labyrinth disorders	5 (2.6)	23 (3.3)	5 (2.7)	34 (3.0)	0	44 (7.8)	7 (6.1)	51 (6.8)	0	1 (0.6)	0	1 (0.4)
Cardiac disorders	15 (7.7)	42 (6.0)	10 (5.3)	67 (6.0)	9 (13.8)	27 (4.8)	4 (3.5)	41 (5.5)	0	4 (2.4)	0	4 (1.7)
Renal and urinary disorders	6 (3.1)	26 (3.7)	5 (2.7)	37 (3.3)	5 (7.7)	33 (5.8)	3 (2.6)	41 (5.5)	1 (2.1)	8 (4.8)	0	9 (3.8)
Metabolism and nutrition disorders	5 (2.6)	69 (9.8)	24 (12.8)	98 (8.8)	2 (3.1)	33 (5.8)	3 (2.6)	38 (5.1)	1 (2.1)	6 (3.6)	3 (12.5)	10 (4.2)
Psychiatric disorders	3 (1.5)	13 (1.9)	6 (3.2)	22 (2.0)	9 (13.8)	25 (4.4)	1 (0.9)	35 (4.7)	0	1 (0.6)	0	1 (0.4)
Reproductive system and breast disorders	2 (1.0)	16 (2.3)	2 (1.1)	21 (1.9)	3 (4.6)	31 (5.5)	1 (0.9)	35 (4.7)	4 (8.5)	4 (2.4)	0	8 (3.4)
Blood and lymphatic system disorders	6 (3.1)	30 (4.3)	14 (7.5)	51 (4.6)	3 (4.6)	21 (3.7)	7 (6.1)	31 (4.1)	1 (2.1)	5 (3.0)	1 (4.2)	7 (3.0)
Hepatobiliary disorders	7 (3.6)	15 (2.1)	4 (2.1)	27 (2.4)	7 (10.8)	14 (2.5)	4 (3.5)	25 (3.3)	4 (8.5)	12 (7.3)	1 (4.2)	17 (7.2)

System organ class	Study 2409				Pool Y1				Study 2402/E Y1			
Blood intake (mL/kg/month)	<7	7-14	>14	All	<7	7-14	>14	All	<7	7-14	>14	All
	n=195	n=701	n=187	N=1115	n=65	n=567	n=114	N=750	n=47	n=165	n=24	N=237
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Vascular disorders	0	9 (1.3)	2 (1.1)	12 (1.1)	5 (7.7)	14 (2.5)	1 (0.9)	20 (2.7)	1 (2.1)	0	0	1 (0.4)
Endocrine disorders	1 (0.5)	12 (1.7)	2 (1.1)	15 (1.3)	2 (3.1)	14 (2.5)	0	16 (2.1)	1 (2.1)	4 (2.4)	1 (4.2)	6 (2.5)
Immune system disorders	1 (0.5)	9 (1.3)	1 (0.5)	11 (1.0)	2 (3.1)	11 (1.9)	1 (0.9)	14 (1.9)	0	1 (0.6)	0	1 (0.4)
Surgical and medical procedures	-	-	-	0	0	7 (1.2)	2 (1.8)	9 (1.2)	0	0	1 (4.2)	1 (0.4)
Neoplasms benign, malignant and unspecified	0	2 (0.3)	0	2 (0.2)	1 (1.5)	3 (0.5)	0	4 (0.5)	1 (2.1)	0	0	1 (0.4)
Congenital disorders	0	0	1 (0.5)	1 (0.1)	0	2 (0.4)	0	2 (0.3)	-	-	-	0
Social circumstances	0	1 (0.1)	0	1 (0.1)	0	0	1 (0.9)	1 (0.1)	-	-	-	0
Pregnancy, puerperium and perinatal conditions	0	1 (0.1)	1 (0.5)	2 (0.2)	-	-	-	0	-	-	-	0

SOCs are presented in descending order of frequency according to the Pool Y1 All column. Blood intake categories: < 7 mL pRBCs/kg/month (low blood intake), 7 to 14 mL pRBCs/kg/month (moderate blood intake), and >14 mL pRBCs/kg/month (high blood intake).
Frequency is the number of patients with AE onset within the given year. N is the number of patients receiving deferasirox at the start of the given year.
A patient with multiple AEs within a primary system organ class is counted only once in the total row.

Table 13 –Frequent AEs (at least 5% in any dataset total) regardless of study drug relationship by blood intake and PT in the first year of treatment (SAS)

Preferred term	Study 2409				Pool Y1				Study 2402/E Y1			
Blood intake (mL/kg/month)	<7	7-14	>14	All	<7	7-14	>14	All	<7	7-14	>14	All
	n=195	n=701	n=187	N=1115	n=65	n=567	n=114	N=750	n=47	n=165	n=24	N=237
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any PT	137 (70.3)	555 (79.2)	161 (86.1)	880 (78.9)	56 (86.2)	522 (92.1)	87 (76.3)	668 (89.1)	38 (80.9)	123 (74.5)	19 (79.2)	181 (76.4)
Pyrexia	16 (8.2)	88 (12.6)	14 (7.5)	124 (11.1)	15 (23.1)	133 (23.5)	27 (23.7)	175 (23.3)	2 (4.3)	6 (3.6)	4 (16.7)	12 (5.1)
Headache	18 (9.2)	52 (7.4)	19 (10.2)	90 (8.1)	12 (18.5)	121 (21.3)	15 (13.2)	148 (19.7)	3 (6.4)	4 (2.4)	0	7 (3.0)
Cough	8 (4.1)	65 (9.3)	14 (7.5)	87 (7.8)	7 (10.8)	120 (21.2)	16 (14.0)	143 (19.1)	1 (2.1)	3 (1.8)	0	4 (1.7)
Diarrhoea	21 (10.8)	85 (12.1)	36 (19.3)	143 (12.8)	17 (26.2)	95 (16.8)	7 (6.1)	119 (15.9)	4 (8.5)	10 (6.1)	0	14 (5.9)
Abdominal pain	10 (5.1)	61 (8.7)	30 (16.0)	103 (9.2)	13 (20.0)	85 (15.0)	15 (13.2)	113 (15.1)	2 (4.3)	10 (6.1)	2 (8.3)	14 (5.9)
Vomiting	8 (4.1)	46 (6.6)	14 (7.5)	69 (6.2)	7 (10.8)	76 (13.4)	13 (11.4)	96 (12.8)	4 (8.5)	21 (12.7)	1 (4.2)	26 (11.0)
Nasopharyngitis	16 (8.2)	61 (8.7)	17 (9.1)	94 (8.4)	9 (13.8)	78 (13.8)	6 (5.3)	93 (12.4)	1 (2.1)	4 (2.4)	1 (4.2)	6 (2.5)
Pharyngitis	13 (6.7)	54 (7.7)	15 (8.0)	83 (7.4)	5 (7.7)	76 (13.4)	12 (10.5)	93 (12.4)	2 (4.3)	10 (6.1)	2 (8.3)	14 (5.9)
Influenza	5 (2.6)	23 (3.3)	5 (2.7)	33 (3.0)	7 (10.8)	72 (12.7)	11 (9.6)	90 (12.0)	4 (8.5)	20 (12.1)	1 (4.2)	25 (10.5)
Nausea	10 (5.1)	55 (7.8)	14 (7.5)	80 (7.2)	12 (18.5)	71 (12.5)	6 (5.3)	89 (11.9)	5 (10.6)	11 (6.7)	1 (4.2)	18 (7.6)
Rhinitis	4 (2.1)	23 (3.3)	6 (3.2)	34 (3.0)	2 (3.1)	61 (10.8)	16 (14.0)	79 (10.5)	0	1 (0.6)	0	1 (0.4)
Oropharyngeal pain	-	-	-	0	10 (15.4)	62 (10.9)	2 (1.8)	74 (9.9)	-	-	-	0
Abdominal pain upper	7 (3.6)	35 (5.0)	10 (5.3)	53 (4.8)	13 (20.0)	55 (9.7)	4 (3.5)	72 (9.6)	4 (8.5)	2 (1.2)	0	6 (2.5)
Back pain	7 (3.6)	29 (4.1)	7 (3.7)	44 (3.9)	7 (10.8)	60 (10.6)	5 (4.4)	72 (9.6)	3 (6.4)	3 (1.8)	0	6 (2.5)
Bronchitis	2 (1.0)	15 (2.1)	6 (3.2)	23 (2.1)	4 (6.2)	53 (9.3)	12 (10.5)	69 (9.2)	1 (2.1)	1 (0.6)	0	2 (0.8)
Blood creatinine increased	11 (5.6)	48 (6.8)	8 (4.3)	68 (6.1)	10 (15.4)	49 (8.6)	3 (2.6)	62 (8.3)	3 (6.4)	6 (3.6)	0	9 (3.8)
Upper respiratory tract infection	18 (9.2)	89 (12.7)	47 (25.1)	154 (13.8)	9 (13.8)	43 (7.6)	7 (6.1)	59 (7.9)	1 (2.1)	4 (2.4)	2 (8.3)	7 (3.0)
Rash	17 (8.7)	87 (12.4)	47 (25.1)	161 (14.4)	7 (10.8)	41 (7.2)	11 (9.6)	59 (7.9)	2 (4.3)	16 (9.7)	2 (8.3)	20 (8.4)
Arthralgia	10 (5.1)	18 (2.6)	5 (2.7)	33 (3.0)	7 (10.8)	41 (7.2)	3 (2.6)	51 (6.8)	1 (2.1)	2 (1.2)		3 (1.3)
Asthenia	3 (1.5)	10 (1.4)	2 (1.1)	17 (1.5)	4 (6.2)	38 (6.7)	7 (6.1)	49 (6.5)	-	-	-	0
Acute tonsillitis	5 (2.6)	3 (0.4)	2 (1.1)	11 (1.0)	2 (3.1)	22 (3.9)	4 (3.5)	28 (3.7)	5 (10.6)	7 (4.2)	3 (12.5)	15 (6.3)
ALT increased	14 (7.2)	72 (10.3)	7 (3.7)	95 (8.5)	2 (3.1)	12 (2.1)	3 (2.6)	17 (2.3)	2 (4.3)	9 (5.5)	2 (8.3)	13 (5.5)
AST increased	11 (5.6)	52 (7.4)	4 (2.1)	67 (6.0)	0	3 (0.5)	3 (2.6)	6 (0.8)	1 (2.1)	3 (1.8)	2 (8.3)	6 (2.5)

PTs are presented in descending order of frequency according to the Pool Y1 All column. Blood intake categories: < 7 mL pRBCs/kg/month (low blood intake), 7 to 14 mL pRBCs/kg/month (moderate blood intake), and >14 mL pRBCs/kg/month (high blood intake).
Frequency is the number of patients with AE onset within the given year. N is the number of patients receiving deferasirox at the start of the given year.
A patient with multiple occurrences of an AE is counted only once in that AE category.

- AEs in subsequent years of treatment

According to the MAH, in the Pool in years 2 to 5 and in Study ICL670A2402/E in years 2 and 3, the overall AE incidence and the incidence of most individuals PTs in infrequently transfused patients tended to be slightly lower than in the overall patient population. However, the number of AEs for individual PTs in infrequently transfused patients was too small to make firm conclusions.

Serious adverse event / deaths / other significant events

- Deaths

A total of 16 deaths on study or within 28 days of study drug discontinuation were reported in the 3 datasets and have previously been reported in the individual study reports.

None of the deaths were suspected to be related to deferasirox treatment. Two deaths occurred in 307 infrequently transfused patients (0.64%) and 14 deaths occurred in 1758 patients (0.79%) who were more frequently transfused.

- Serious Adverse Events (SAEs)

Table 14 –Frequent SAEs (more than 2 patients in any dataset total) regardless of study drug relationship by blood intake and PT in the first year of treatment (SAS)

Preferred term	Study 2409				Pool Y1				Study 2402/E Y1			
Blood intake (mL/kg/month)	<7 n=195 n (%)	7-14 n=701 n (%)	>14 n=187 n (%)	All N=1115 n (%)	<7 n=65 n (%)	7-14 n=567 n (%)	>14 n=114 n (%)	All N=750 n (%)	<7 n=47 n (%)	7-14 n=165 n (%)	>14 n=24 n (%)	All N=237 n (%)
Patient with any SAE	17 (8.7)	60 (8.6)	15 (8.0)	97 (8.7)	10 (15.4)	50 (8.8)	6 (5.3)	67 (8.9)	7 (14.9)	8 (4.8)	2 (8.3)	17 (7.2)
Pyrexia	4 (2.1)	5 (0.7)	0	11 (1.0)	1 (1.5)	4 (0.7)	1 (0.9)	6 (0.8)	0	1 (0.6)	0	1 (0.4)
Abdominal pain	0	4 (0.6)	1 (0.5)	5 (0.4)	0	4 (0.7)	0	4 (0.5)	1 (2.1)	0	0	1 (0.4)
Gastroenteritis	1 (0.5)	1 (0.1)	3 (1.6)	5 (0.4)	0	4 (0.7)	0	4 (0.5)	1 (2.1)	0	0	1 (0.4)
Cholelithiasis	1 (0.5)	1 (0.1)	0	2 (0.2)	2 (3.1)	1 (0.2)	1 (0.9)	4 (0.5)	0	1 (0.6)	1 (4.2)	2 (0.8)
Hypersplenism	-	-	-	0	1 (1.5)	1 (0.2)	2 (1.8)	4 (0.5)	-	-	-	0
Femur fracture	-	-	-	0	0	2 (0.4)	0	3 (0.4)	-	-	-	0
Renal colic	0	1 (0.1)	0	1 (0.1)	0	3 (0.5)	0	3 (0.4)	-	-	-	0
Diarrhoea	0	3 (0.4)	1 (0.5)	4 (0.4)	-	-	-	0	1 (2.1)	0	0	1 (0.4)
Cholecystitis acute	1 (0.5)	2 (0.3)	0	4 (0.4)	-	-	-	0	0	2 (1.2)	0	2 (0.8)
Viral infection	0	4 (0.6)	0	4 (0.4)	-	-	-	0	-	-	-	0
Upper respiratory tract infection	0	3 (0.4)	0	3 (0.3)	-	-	-	0	-	-	-	0
Diabetic ketoacidosis	1 (0.5)	1 (0.1)	1 (0.5)	3 (0.3)	-	-	-	0	-	-	-	0

PTs are presented in descending order of frequency according to the Pool Y1 All column. Blood intake categories: <7 mL pRBCs/kg/month (low blood intake), 7 to 14 mL pRBCs/kg/month (moderate blood intake), and >14 mL pRBCs/kg/month (high blood intake).
Frequency is the number of patients with AE onset within the given year. N is the number of patients receiving deferasirox at the start of the given year.
A patient with multiple occurrences of an AE is counted only once in that AE category.

Table 15 –Frequent SAEs (more than 2 patients in any dataset total) regardless of study drug relationship by blood intake and PT in Pool Years 2 to 5 and Study 2402 Years 2 and 3 (SAS)

Preferred term	Pool Y2		Pool Y3		Pool Y4		Pool Y5		Study 2402 Y2		Study 2402 Y3	
Blood intake (mL/kg/month)	<7 n=74 n (%)	All N=682 n (%)	<7 n=76 n (%)	All N=609 n (%)	<7 n=78 n (%)	All N=551 n (%)	<7 n=47 n (%)	All N=315 n (%)	<7 n=61 n (%)	All N=231 n (%)	<7 n=48 n (%)	All N=217 n (%)
Patient with any SAE	9 (12.2)	72 (10.6)	9 (11.8)	58 (9.5)	11 (14.1)	54 (9.8)	5 (10.6)	31 (9.8)	6 (9.8)	13 (5.6)	1 (2.1)	6 (2.8)
Abdominal pain	1 (1.4)	5 (0.7)	1 (1.3)	2 (0.3)	1 (1.3)	4 (0.7)	0	1 (0.3)	-	0	-	0
Pyrexia	0	5 (0.7)	2 (2.6)	4 (0.7)	2 (2.6)	4 (0.7)	0	1 (0.3)	-	0	-	0
Hypersplenism	0	5 (0.7)	0	4 (0.7)	0	1 (0.2)	-	0	-	0	-	0
Cholelithiasis	0	1 (0.1)	1 (1.3)	5 (0.8)	2 (2.6)	6 (1.1)	-	0	-	0	-	0
Abdominal pain upper	0	1 (0.1)	0	1 (0.2)	1 (1.3)	1 (0.2)	-	0	1 (1.6)	3 (1.3)	-	0
Road traffic accident	0	1 (0.1)	0	1 (0.2)	-	0	1 (2.1)	1 (0.3)	1 (1.6)	2 (0.9)	-	0
Splenomegaly	0	1 (0.1)	0	1 (0.2)	1 (1.3)	2 (0.4)	0	3 (1.0)	-	0	-	0
Upper limb fracture	-	0	-	0	-	0	-	0	2 (3.3)	2 (0.9)	0	1 (0.5)
Transaminases increased	-	4 (0.6)	-	0	-	0	-	0	-	0	-	0

PTs are presented in descending order of frequency according to the Pool Y2 All column. Only the <7 mL/kg/month blood intake category is presented here.
Frequency is the number of patients with AE onset within the given year. N is the number of patients receiving deferasirox at the start of the given year.
A patient with multiple occurrences of an AE is counted only once in that AE category.

- AEs of special interest

Group term AEs for rash, nausea/vomiting, abdominal pain, and diarrhoea were the most frequently reported in all datasets. Most of these AEs were mild to moderate in severity, rarely reported as SAEs, and infrequently resulted in study drug discontinuation.

No clear pattern in the frequencies of AEs of special interest by blood intake groups could be delineated across the 3 datasets. In the 2409 and 2402/E datasets, rash was more frequently reported in frequently transfused patients. However, in the Pool dataset, abdominal pain, diarrhoea, and abnormal

blood creatinine were more commonly reported in infrequently transfused patients. No cases of Fanconi syndrome or hearing loss were reported in infrequently transfused patients. Across all 3 datasets, only one patient, in the moderate blood intake category, presented with a liver function impairment group term AE. All other AEs of special interest were of similar frequencies by blood intake groups.

Table 16 – Adverse event of special interest by blood intake and PT in the first year of treatment (SAS)

AESI group	Study 2409				Pool Y1				Study 2402/E Y1			
Blood intake (mL/kg/month)	<7	7-14	>14	All	<7	7-14	>14	All	<7	7-14	>14	All
	n=195	n=701	n=187	N=1115	n=65	n=567	n=114	N=750	n=47	n=165	n=24	N=237
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Abdominal pain	24 (12.3)	93 (13.3)	41 (21.9)	162 (14.5)	23 (35.4)	149 (26.3)	21 (18.4)	193 (25.7)	5 (10.6)	13 (7.9)	2 (8.3)	21 (8.9)
Nausea and vomiting	14 (7.2)	80 (11.4)	22 (11.8)	118 (10.6)	15 (23.1)	123 (21.7)	16 (14.0)	154 (20.5)	7 (14.9)	28 (17.0)	2 (8.3)	38 (16.0)
Diarrhoea	21 (10.8)	85 (12.1)	36 (19.3)	143 (12.8)	17 (26.2)	94 (16.6)	7 (6.1)	118 (15.7)	4 (8.5)	10 (6.1)	0	14 (5.9)
Rash	24 (12.3)	105 (15.0)	58 (31.0)	199 (17.8)	10 (15.4)	58 (10.2)	14 (12.3)	84 (11.2)	2 (4.3)	19 (11.5)	4 (16.7)	25 (10.5)
Abnormal blood creatinine	15 (7.7)	59 (8.4)	9 (4.8)	84 (7.5)	10 (15.4)	50 (8.8)	4 (3.5)	64 (8.5)	3 (6.4)	6 (3.6)	0	9 (3.8)
Transaminase increased	15 (7.7)	91 (13.0)	12 (6.4)	120 (10.8)	3 (4.6)	27 (4.8)	6 (5.3)	36 (4.8)	2 (4.3)	9 (5.5)	2 (8.3)	13 (5.5)
Proteinuria	5 (2.6)	8 (1.1)	2 (1.1)	15 (1.3)	0	14 (2.5)	1 (0.9)	15 (2.0)	3 (6.4)	7 (4.2)	0	10 (4.2)
Hearing loss	0	1 (0.1)	0	1 (0.1)	0	8 (1.4)	2 (1.8)	10 (1.3)	-	-	-	0
Cataract and lenticular opacities	-	-	-	0	1 (1.5)	5 (0.9)	0	6 (0.8)	-	-	-	0
GI ulcer or bleeding	2 (1.0)	1 (0.1)	1 (0.5)	4 (0.4)	0	2 (0.4)	1 (0.9)	3 (0.4)	1 (2.1)	0	0	1 (0.4)
Fanconi syndrome	0	1 (0.1)	1 (0.5)	2 (0.2)	0	0	1 (0.9)	1 (0.1)	-	-	-	0
Liver function impairment	0	1 (0.1)	0	1 (0.1)	-	-	-	0	-	-	-	0
Renal function impairment	1 (0.5)	1 (0.1)	0	2 (0.2)	-	-	-	0	0	1 (0.6)	0	1 (0.4)

Blood intake categories: < 7 mL pRBCs/kg/month (low blood intake), 7 to 14 mL pRBCs/kg/month (moderate blood intake), and >14 mL pRBCs/kg/month (high blood intake).
Frequency is the number of patients with AE onset within the given year. N is the number of patients receiving deferasirox at the start of the given year.
A patient with multiple occurrences of an AE is counted only once in that AE category. A patient with multiple AEs within an AESI group is counted only once in the total row

In subsequent years of treatment, diarrhoea and abnormal blood creatinine were more common in frequently transfused patients than in those infrequently transfused in Years 2 to 4, with similar frequencies for these AESIs between blood intake groups in Year 5. Abdominal pain was more common in frequently transfused patients than in infrequently transfused patients in Year 2; however, this trend was reversed in Year 3, with a similar frequency of this AE of special interest between both blood intake groups in Years 4 and Year 5. All other AEs of special interest were similar in incidence between blood intake groups throughout all time points.

- Long-term use

Table 17 – Incidence of AR categories by blood intake in subsequent years of treatment (SAS)

Preferred term	Pool Y2		Pool Y3		Pool Y4		Pool Y5		2402 Y2		2402 Y3	
Blood intake (mL pRBCs/kg/month)	<7	All	<7	All	<7	All	<7	All	<7	All	<7	All
	n=74	N=682	n=76	N=609	n=78	N=551	n=47	N=315	n=61	N=231	n=48	N=217
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Overall AEs	57 (77.0)	556 (81.5)	64 (84.2)	491 (80.6)	57 (73.1)	432 (78.4)	31 (66.0)	233 (74.0)	31 (50.8)	128 (55.4)	10 (20.8)	62 (28.6)
Severe AEs	3 (4.1)	44 (6.5)	5 (6.6)	38 (6.2)	8 (10.3)	37 (6.7)	2 (4.3)	18 (5.7)	6 (9.8)	13 (5.6)	1 (2.1)	4 (1.8)
Drug-related AEs	18 (24.3)	109 (16.0)	12 (15.8)	84 (13.8)	10 (12.8)	76 (13.8)	2 (4.3)	26 (8.3)	16 (26.2)	48 (20.8)	2 (4.2)	11 (5.1)
SAEs	9 (12.2)	72 (10.6)	9 (11.8)	58 (9.5)	11 (14.1)	54 (9.8)	5 (10.6)	31 (9.8)	6 (9.8)	13 (5.6)	1 (2.1)	6 (2.8)
AEs leading to discontinuation	1 (1.4)	27 (4.0)	1 (1.3)	17 (2.8)	1 (1.3)	8 (1.5)	0	6 (1.9)	1 (1.6)	4 (1.7)	0	0

Laboratory findings

The mean and relative change from baseline to last value in the first year of treatment is summarised in Table 18 for ALT, serum creatinine, CrCl, and UPCR. Select laboratory parameters are categorised at the end of the first year of treatment and are presented in Table 19.

Table 18 – Mean absolute and relative biochemistry change from baseline to end of first year by blood intake (SAS)

Blood intake (mL/kg/month)	Study 2409 <7	7-14	>14	All	Pool Y1 <7	7-14	>14	All	Study 2402/E Y1 <7	7-14	>14	All
	n=195	n=701	n=187	N=1115	n=65	n=567	n=114	N=750	n=47	n=165	n=24	N=237
ALT (U/L) – mean (SD)												
	n=191	n=683	n=185	n=1091	n=65	n=565	n=114	n=748	n=47	n=164	n=24	n=236
Mean at baseline	71.8 (59.02)	62.5 (54.99)	46.5 (50.94)	61.1 (55.07)	60.0 (46.12)	47.6 (51.03)	32.5 (29.15)	46.8 (49.24)	62.1 (41.39)	61.0 (52.67)	90.9 (64.12)	64.1 (52.44)
Mean absolute change	-25.8 (50.7)	-5.4 (62.9)	7.6 (113.4)	-6.9 (72.7)	-1.2 (51.5)	8.3 (52.1)	26.1 (62.5)	10.2 (54.1)	0 (51.1)	-0.1 (59.8)	2.8 (63.5)	0.2 (58.2)
Mean relative % change	-19.5 (83.8)	19.7 (174.2)	68.5 (326.3)	20.7 (198.9)	17.9 (98.5)	56.9 (146.5)	160.9 (370.1)	69.3 (198.7)	6.7% (83.3)	53.0 (195.7)	35.4 (160.9)	41.9 (175.6)
Serum creatinine (umol/L) – mean (SD)												
	n=194	n=691	n=186	n=1103	n=65	n=565	n=114	n=748	n=47	n=164	n=24	n=236
Mean at baseline	42.8 (11.91)	41.1 (14.38)	44.4 (13.39)	42.3 (14.00)	48.1 (13.22)	47.3 (14.83)	42.8 (14.74)	46.7 (14.73)	42.4 (9.78)	37.7 (12.52)	34.2 (8.28)	38.4 (11.86)
Mean absolute change	9.3 (11.6)	8.1 (10.5)	9.6 (11.3)	8.5 (10.9)	8.5 (10.1)	8.6 (11.0)	7.8 (10.3)	8.5 (10.1)	7.1 (9.6)	6.3 (10.4)	3.0 (7.7)	6.2 (10.0)
Mean relative % change	23.5 (28.1)	22.4 (27.0)	23.6 (28.8)	22.6 (27.5)	19.2 (22.8)	20.6 (23.4)	22.9 (35.0)	20.8 (25.5)	17.3 (21.3)	20.7 (31.6)	9.5 (20.4)	18.9 (28.9)
Creatinine clearance (mL/min) – mean (SD)												
	n=194	n=701	n=187	n=1114	n=65	n=567	n=114	n=750	n=47	n=164	n=24	n=236
Mean at baseline	177.7 (51.88)	174.4 (54.81)	158.9 (48.91)	171.4 (53.67)	173.0 (52.74)	158.9 (52.88)	164.1 (53.30)	160.9 (52.90)	185.3 (38.81)	187.3 (55.62)	174.7 (29.33)	185.3 (50.59)
Mean absolute change	-25.2 (40.4)	-23.7 (38.7)	-22.7 (33.8)	-23.6 (38.1)	-23.0 (34.6)	-20.9 (33.1)	-22.2 (38.1)	-21.3 (34.0)	-19.6 (32.2)	-19.0 (47.2)	-1.8 (33.4)	-17.4 (43.4)
Mean relative % change	-12.7 (20.3)	-12.1 (20.3)	-12.9 (18.4)	-12.2 (20.0)	-12.0 (16.9)	-11.4 (18.3)	-11.6 (18.6)	-11.5 (18.3)	-9.6 (17.7)	-7.5 (23.2)	0.1 (22.2)	-7.2 (22.1)
Urine protein/creatinine ratio (mg/mg) – mean (SD)												
	n=102	n=334	n=124	n=579	n=65	n=560	n=114	n=743	n=47	n=165	n=24	n=237
Mean at baseline	0.3 (0.26)	0.3 (0.19)	0.2 (0.15)	0.3 (0.21)	0.2 (0.26)	0.2 (0.10)	0.2 (0.12)	0.2 (0.12)	0.2 (0.10)	0.2 (0.09)	0.3 (0.07)	0.2 (0.09)
Mean absolute change	0.0 (0.3)	0.0 (0.2)	0.0 (0.16)	0.0 (0.2)	0.0 (0.2)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)
Mean relative % change	10.3 (45.4)	22.4 (209.7)	33.7 (87.7)	23.0 (167.6)	21.1 (72.4)	19.3 (122.9)	16.5 (63.3)	19.1 (111.7)	19.1 (65.4)	21.2 (80.5)	4.0 (46.9)	18.8 (74.8)

The mean absolute value change is presented with the standard deviation. The mean relative % change from baseline is presented with the standard deviation.

Table 19 – Categorised laboratory parameters by blood intake at to end of first year of treatment (SAS)

Blood intake (mL/kg/month)	Study 2409 <7	7-14	>14	All	Pool Y1 <7	7-14	>14	All	Study 2402/E Y1 <7	7-14	>14	All
	n=195	n=701	n=187	N=1115	n=65	n=567	n=114	N=750	n=47	n=165	n=24	N=237
ALT (U/L) – n (%)	n=194	n=700	n=187	n=1096	n=65	n=567	n=113	n=745	n=47	n=165	n=24	n=237
≤ 5xULN	192 (99.0)	660 (94.3)	180 (96.3)	1047 (95.5)	63 (96.9)	553 (97.5)	109 (96.5)	725 (97.3)	45 (95.7)	158 (95.8)	20 (83.3)	224 (94.5)
>5x and ≤ 10xULN	1 (0.5)	33 (4.7)	5 (2.7)	39 (3.6)	2 (3.1)	12 (2.1)	3 (2.7)	17 (2.3)	1 (2.1)	7 (4.2)	4 (16.7)	12 (5.1)
>10xULN	1 (0.5)	7 (1.0)	2 (1.1)	10 (0.9)	0	2 (0.4)	1 (0.9)	3 (0.4)	1 (2.1)	0	0	1 (0.4)
CrCl (mL/min) – n (%)	n=194	n=700	n=187	n=1096	n=65	n=567	n=114	n=746	n=47	n=165	n=24	n=237
<40	-	-	-	0	-	-	-	0	-	-	-	0
40 to <60	3 (1.5)	4 (0.6)	2 (1.1)	10 (0.9)	0	2 (0.4)	0	2 (0.3)	0	0	0	0
60 to <90	13 (6.7)	55 (7.9)	24 (12.8)	95 (8.7)	5 (7.7)	72 (12.7)	17 (14.9)	94 (12.6)	1 (2.1)	4 (2.4)	0	5 (2.1)
90 to <160	108 (55.7)	372 (53.1)	111 (59.4)	598 (54.6)	40 (61.5)	333 (58.7)	62 (54.4)	435 (58.3)	21 (44.7)	73 (44.2)	9 (37.5)	104 (43.9)
≥ 160	70 (36.1)	269 (38.4)	50 (26.7)	393 (35.9)	20 (30.8)	160 (28.2)	35 (30.7)	215 (28.8)	25 (53.2)	88 (53.3)	15 (62.5)	128 (54.0)
UPCR (%) – n (%)	n=119	n=387	n=131	n=647	n=65	n=567	n=114	n=747	n=47	n=165	n=24	n=237
<0.2	20 (16.8)	114 (29.5)	64 (48.9)	202 (31.2)	36 (55.4)	378 (66.7)	69 (60.5)	484 (64.8)	16 (34.0)	66 (40.0)	5 (20.8)	88 (37.1)
0.2 to 0.5	79 (66.4)	211 (54.5)	50 (38.2)	345 (53.3)	26 (40.0)	175 (30.9)	43 (37.7)	244 (32.7)	30 (63.8)	91 (55.2)	19 (79.2)	140 (59.1)
>0.5 to 1.0	11 (9.2)	46 (11.9)	14 (10.7)	71 (11.0)	2 (3.1)	13 (2.3)	2 (1.8)	17 (2.3)	1 (2.1)	8 (4.8)	0	9 (3.8)
>1.0	4 (3.4)	0	1 (0.8)	5 (0.8)	1 (1.5)	1 (0.2)	0	2 (0.3)	-	-	-	0
Missing	5 (4.2)	16 (4.1)	2 (1.5)	24 (3.7)	-	-	-	0	-	-	-	0

- Renal parameters

Creatinine clearance (CrCl)

The relative changes in CrCl by age group (extended pooled safety set) are detailed in the table below:

Table 20 – Relative change in Creatinine Clearance (Extended Pooled Safety Set)

Relative change from baseline (Year 1) or from previous year in creatinine clearance (%)		Blood intake < 7 mL/kg/month	Blood intake ≥ 7 mL/kg/month	All Patients
Year 1 any dose group	Mean (n)	-7.90 (n=108)	-10.08 (n=1034)	-9.87 (n=1142)
age <18	95% CI	-12.21, -3.59	-11.36, -8.79	-11.10, -8.64
Year 1 any dose group	Mean (n)	-13.69 (n=213)	-13.11 (n=722)	-13.24 (n=935)
age ≥ 18	95% CI	-15.97, -11.40	-14.41, -11.81	-14.37, -12.11
Year 2 any dose group	Mean (n)	3.83 (n=56)	2.64 (n=464)	2.77 (n=520)
age <18	95% CI	-2.70, 10.35	0.56, 4.73	0.79, 4.75
Year 2 any dose group	Mean (n)	-0.36 (n=85)	0.99 (n=303)	0.69 (n=388)
age ≥ 18	95% CI	-4.67, 3.95	-1.03, 3.00	-1.14, 2.52
Year 3 any dose group	Mean (n)	1.16 (n=61)	3.12 (n=424)	2.87 (n=485)
age <18	95% CI	-3.52, 5.85	1.18, 5.06	1.08, 4.67
Year 3 any dose group	Mean (n)	3.34 (n=74)	0.20 (n=253)	0.91 (n=327)
age ≥ 18	95% CI	-1.83, 8.51	-1.71, 2.10	-0.97, 2.78
Year 4 any dose group	Mean (n)	-1.12 (n=29)	5.26 (n=235)	4.56 (n=264)
age <18	95% CI	-7.51, 5.27	2.77, 7.74	2.24, 6.87
Year 4 any dose group	Mean (n)	6.18 (n=48)	3.22 (n=167)	3.88 (n=215)
age ≥ 18	95% CI	1.68, 10.68	0.79, 5.64	1.75, 6.00
Year 5 any dose group	Mean (n)	9.03 (n=13)	4.82 (n=123)	5.22 (n=136)
age <18	95% CI	-1.26, 19.32	1.63, 8.00	2.21, 8.23
Year 5 any dose group	Mean (n)	5.50 (n=32)	1.85 (n=82)	2.87 (n=114)
age ≥ 18	95% CI	1.18, 9.81	-1.44, 5.15	0.23, 5.52

Safety in special populations

For the purposes of this analysis, the safety profiles of deferasirox in infrequently transfused patients versus frequently transfused patients were compared across defined age and average daily dose subgroups.

Table 21 – Frequency of AE categories by blood intake and age in the first year of treatment (SAS)

	Study 2409				Pool Y1				Study 2402/E Y1			
Age (years)	<6	6 - <12	12 - <18	≥ 18	<6	6 - <12	12 - <18	≥ 18	<6	6 - <12	12 - <18	≥ 18
Blood Intake in pRBCs	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any blood intake	**n=130**	**n=215**	**n=253**	**n=517**	**n=56**	**n=143**	**n=172**	**n=379**	**n=27**	**n=76**	**n=79**	**n=55**
Overall AEs	87 (66.9)	159 (74.0)	193 (76.3)	441 (85.3)	50 (89.3)	120 (83.9)	146 (84.9)	352 (92.9)	22 (81.5)	56 (73.7)	57 (72.2)	46 (83.6)
Severe AEs	6 (4.6)	17 (7.9)	21 (8.3)	61 (11.8)	1 (1.8)	8 (5.6)	13 (7.6)	47 (12.4)	0	4 (5.3)	1 (1.3)	13 (23.6)
Drug related AEs	46 (35.4)	78 (36.3)	90 (35.6)	273 (52.8)	13 (23.2)	38 (26.6)	52 (30.2)	170 (44.9)	8 (29.6)	32 (42.1)	39 (49.4)	26 (47.3)
SAEs	8 (6.2)	13 (6.0)	18 (7.1)	58 (11.2)	5 (8.9)	11 (7.7)	12 (7.0)	39 (10.3)	0	4 (5.3)	3 (3.8)	10 (18.2)
AEs leading to disc.	5 (3.8)	4 (1.9)	4 (1.6)	31 (6.0)	0	3 (2.1)	6 (3.5)	12 (3.2)	0	0	0	2 (3.6)
<7 mL/kg/month	**n=2**	**n=21**	**n=46**	**n=126**	**n=0**	**n=4**	**n=13**	**n=48**	**n=0**	**n=6**	**n=14**	**n=27**
Overall AEs	2 (100)	13 (61.9)	28 (60.9)	94 (74.6)	-	2 (50.0)	8 (61.5)	46 (95.8)	-	6 (100)	11 (78.6)	21 (77.8)
Severe AEs	0	0	0	13 (10.3)	-	0	2 (15.4)	11 (22.9)	-	2 (33.3)	0	7 (25.9)
Drug related AEs	2 (100)	5 (23.8)	15 (32.6)	46 (36.5)	-	1 (25.0)	2 (15.4)	27 (56.3)	-	2 (33.3)	8 (57.1)	13 (48.1)
SAEs	0	1 (4.8)	2 (4.3)	14 (11.1)	-	0	2 (15.4)	8 (16.7)	-	2 (33.3)	1 (7.1)	4 (14.8)
AEs leading to disc.	0	0	0	2 (1.6)	-	0	0	2 (4.2)	-	-	-	0
7-14 mL/kg/month	**n=111**	**n=151**	**n=147**	**n=292**	**n=32**	**n=101**	**n=138**	**n=296**	**n=21**	**n=56**	**n=63**	**n=25**
Overall AEs	71 (64.0)	110 (72.8)	113 (76.9)	261 (89.4)	31 (96.9)	89 (88.1)	122 (88.4)	280 (94.6)	17 (81.0)	40 (71.4)	44 (69.8)	22 (88.0)
Severe AEs	5 (4.5)	13 (8.6)	14 (9.5)	34 (11.6)	1 (3.1)	6 (5.9)	11 (8.0)	35 (11.8)	-	1 (1.8)	1 (1.6)	6 (24.0)
Drug related AEs	36 (32.4)	55 (36.4)	47 (32.0)	170 (58.2)	6 (18.8)	25 (24.8)	49 (35.5)	130 (43.9)	5 (23.8)	24 (42.9)	30 (47.6)	11 (44.0)
SAEs	7 (6.3)	8 (5.3)	13 (8.8)	32 (11.0)	3 (9.4)	8 (7.9)	10 (7.2)	29 (9.8)	-	1 (1.8)	1 (1.6)	6 (24.0)
AEs leading to disc.	1 (0.9)	2 (1.3)	1 (0.7)	15 (5.1)	-	2 (2.0)	6 (4.3)	7 (2.4)	-	-	-	2 (8.0)
>14 mL/kg/month	**n=17**	**n=38**	**n=56**	**n=76**	**n=24**	**n=37**	**n=21**	**n=32**	**n=6**	**n=14**	**n=2**	**n=2**
Overall AEs	14 (82.4)	33 (86.8)	48 (85.7)	66 (86.8)	19 (79.2)	28 (75.7)	16 (76.2)	24 (75.0)	5 (83.3)	10 (71.4)	2 (100)	2 (100)
Severe AEs	1 (5.9)	3 (7.9)	6 (10.7)	9 (11.8)	0	2 (5.4)	0	0	-	1 (7.1)	0	0
Drug related AEs	8 (47.1)	15 (39.5)	24 (42.9)	41 (53.9)	7 (29.2)	11 (29.7)	1 (4.8)	12 (37.5)	3 (50.0)	6 (42.9)	1 (50.0)	1 (50.0)
SAEs	1 (5.9)	2 (5.3)	3 (5.4)	9 (11.8)	2 (8.3)	3 (8.1)	0	1 (3.1)	-	1 (7.1)	1 (50.0)	0
AEs leading to disc.	4 (23.5)	0	1 (1.8)	4 (5.3)	-	0	0	1 (3.1)	-	-	-	0

- Average daily dose

Table 22 – Incidence of AE categories by blood intake and average daily dose in the first year of treatment (SAS)

	Study 2409						Pool Y1						Study 2402/E Y1					
Dose group (mg/kg/day)	<7.5	7.5-12.5	>12.5-17.5	>17.5 - <25	25 -<35	≥ 35	<7.5	7.5-12.5	>12.5-17.5	>17.5 - <25	25 -<35	≥ 35	<7.5	7.5-12.5	>12.5-17.5	>17.5 - <25	25 -<35	≥ 35
Blood Intake	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any blood intake	**n=4**	**n=19**	**n=46**	**n=580**	**n=418**	**n=48**	**n=17**	**n=163**	**n=121**	**n=245**	**n=203**	**n=1**	**n=0**	**n=0**	**n=11**	**n=148**	**n=78**	**n=0**
Overall AEs	4 (100)	18 (94.7)	42 (91.3)	438 (75.5)	343 (82.1)	35 (72.9)	17 (100)	151 (92.6)	115 (95.0)	213 (86.9)	171 (84.2)	1 (100)	-	-	11 (100)	103 (69.6)	67 (85.9)	-
Severe AEs	2 (50.0)	4 (21.1)	11 (23.9)	43 (7.4)	39 (9.3)	6 (12.5)	1 (5.9)	20 (12.3)	13 (10.7)	14 (5.7)	21 (10.3)	0	-	-	0	10 (6.8)	8 (10.3)	-
Drug related AEs	4 (100)	14 (73.7)	27 (58.7)	248 (42.8)	174 (41.6)	20 (41.7)	9 (52.9)	46 (28.2)	44 (36.4)	85 (34.7)	89 (43.8)	0	-	-	9 (81.8)	55 (37.2)	41 (52.6)	-
SAEs	1 (25.0)	1 (5.3)	8 (17.4)	54 (9.3)	29 (6.9)	4 (8.3)	2 (11.8)	11 (6.7)	15 (12.4)	21 (8.6)	18 (8.9)	0	-	-	0	8 (5.4)	9 (11.5)	-
AEs leading to disc.	2 (50.0)	9 (47.4)	8 (17.4)	18 (3.1)	7 (1.7)	0	2 (11.8)	8 (4.9)	3 (2.5)	4 (1.6)	4 (2.0)	0	-	-	0	2 (1.4)	0	-
<7 mL/kg/month	**n=0**	**n=7**	**n=9**	**n=106**	**n=59**	**n=14**	**n=1**	**n=10**	**n=11**	**n=17**	**n=26**	**n=0**	**n=0**	**n=0**	**n=2**	**n=33**	**n=12**	**n=0**
Overall AEs	-	6 (85.7)	8 (88.9)	75 (70.8)	42 (71.2)	6 (42.9)	1 (100)	9 (90.0)	9 (81.8)	16 (94.1)	21 (80.8)	-	-	-	2 (100)	26 (78.8)	10 (83.3)	-
Severe AEs	-	1 (14.3)	1 (11.1)	7 (6.6)	4 (6.8)	0	0	1 (10.0)	2 (18.2)	2 (11.8)	8 (30.8)	-	-	-	-	5 (15.2)	4 (33.3)	-
Drug related AEs	-	4 (57.1)	3 (33.3)	41 (38.7)	18 (30.5)	2 (14.3)	0	3 (30.0)	2 (18.2)	12 (70.6)	13 (50.0)	-	-	-	2 (100)	16 (48.5)	5 (41.7)	-
SAEs	-	0	1 (11.1)	12 (11.3)	3 (5.1)	1 (7.1)	1 (100)	0	1 (9.1)	2 (11.8)	6 (23.1)	-	-	-	-	4 (12.1)	3 (25.0)	-
AEs leading to disc.	-	1 (14.3)	0	1 (0.9)	0	-	0	1 (10.0)	0	0	1 (3.8)	-	-	-	-	0	-	-

	Study 2409						Pool Y1						Study 2402/E Y1					
Dose group (mg/kg/day)	<7.5	7.5-12.5	>12.5-17.5	>17.5 - <25	25 -<35	≥ 35	<7.5	7.5-12.5	>12.5-17.5	>17.5 - <25	25 -<35	≥ 35	<7.5	7.5-12.5	>12.5-17.5	>17.5 - <25	25 -<35	≥ 35
Blood Intake	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
7-14 mL/kg/month	**n=1**	**n=5**	**n=25**	**n=362**	**n=280**	**n=28**	**n=13**	**n=126**	**n=93**	**n=182**	**n=152**	**n=1**	**n=0**	**n=0**	**n=8**	**n=99**	**n=58**	**n=0**
Overall AEs	1 (100)	5 (100)	23 (92.0)	271 (74.9)	232 (82.9)	23 (82.1)	13 (100)	119 (94.4)	91 (97.8)	165 (90.7)	133 (87.5)	1 (100)	-	-	8 (100)	66 (66.7)	49 (84.5)	-
Severe AEs	0	1 (20.0)	6 (24.0)	29 (8.0)	26 (9.3)	4 (14.3)	1 (7.7)	19 (15.1)	10 (10.8)	11 (6.0)	12 (7.9)	-	-	-	-	5 (5.1)	3 (5.2)	-
Drug related AEs	1 (100)	4 (80.0)	15 (60.0)	152 (42.0)	123 (43.9)	13 (46.4)	7 (53.8)	38 (30.2)	37 (39.8)	61 (33.5)	67 (44.1)	-	-	-	6 (75.0)	33 (33.3)	31 (53.4)	-
SAEs	0	1 (20.0)	5 (20.0)	34 (9.4)	18 (6.4)	2 (7.1)	1 (7.7)	11 (8.7)	12 (12.9)	15 (8.2)	11 (7.2)	-	-	-	-	4 (4.0)	4 (6.9)	-
AEs leading to disc.	0	3 (60.0)	5 (20.0)	9 (2.5)	2 (0.7)	-	1 (7.7)	5 (4.0)	3 (3.2)	3 (1.6)	3 (2.0)	-	-	-	-	2 (2.0)	-	-
>14 mL/kg/month	**n=1**	**n=2**	**n=8**	**n=92**	**n=78**	**n=6**	**n=3**	**n=25**	**n=17**	**n=44**	**n=25**	**n=0**	**n=0**	**n=0**	**n=1**	**n=15**	**n=8**	**n=0**
Overall AEs	1 (100)	2 (100)	7 (87.5)	77 (83.7)	68 (87.2)	6 (100)	3 (100)	21 (84.0)	15 (88.2)	31 (70.5)	17 (68.0)	-	-	-	1 (100)	10 (66.7)	8 (100)	-
Severe AEs	1 (100)	0	2 (25.0)	5 (5.4)	9 (11.5)	2 (33.3)	0	0	1 (5.9)	0	1 (4.0)	-	-	-	-	0	1 (12.5)	-
Drug related AEs	1 (100)	2 (100)	5 (62.5)	43 (46.7)	32 (41.0)	5 (83.3)	2 (66.7)	3 (12.0)	5 (29.4)	12 (27.3)	9 (36.0)	-	-	-	1 (100)	5 (33.3)	5 (62.5)	-
SAEs	1 (100)	0	0	5 (5.4)	8 (10.3)	1 (16.7)	0	0	2 (11.8)	3 (6.8)	1 (4.0)	-	-	-	-	0	2 (25.0)	-
AEs leading to disc.	0	1 (50.0)	0	3 (3.3)	5 (6.4)	-	1 (33.3)	0	0	0	0	-	-	-	-	0	-	-

Blood intake categories: < 7 mL pRBCs/kg/month (low blood intake), 7 to 14 mL pRBCs/kg/month (moderate blood intake), and >14 mL pRBCs/kg/month (high blood intake).

Discontinuation due to adverse events

Table 23 – Frequent AEs leading to discontinuation (at least 2 patients in any dataset total) by blood intake and PT in the first year of treatment (SAS)

Preferred term	Study 2409				Pool Y1				Study 2402/E Y1			
Blood intake (mL/kg/month)	<7	7-14	>14	All	<7	7-14	>14	All	<7	7-14	>14	All
	n=195	n=701	n=187	N=1115	n=65	n=567	n=114	N=750	n=47	n=165	n=24	N=237
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with any AE leading to disc.	2 (1.0)	19 (2.7)	9 (4.8)	44 (3.9)	2 (3.1)	15 (2.6)	1 (0.9)	21 (2.8)	0	2 (1.2)	0	2 (0.8)
ALT increased	0	0	1 (0.5)	1 (0.1)	0	3 (0.5)	0	3 (0.4)	-	-	-	0
Transaminases increased	0	1 (0.1)	2 (1.1)	3 (0.3)	1 (1.5)	2 (0.4)	0	3 (0.4)	-	-	-	0
Pyrexia	0	0	0	2 (0.2)	0	2 (0.4)	0	2 (0.3)	-	-	-	0
Rash pruritic	-	-	-	0	0	0	0	2 (0.3)	-	-	-	0
Cardiac failure	0	2 (0.3)	0	2 (0.2)	0	1 (0.2)	0	1 (0.1)	-	2 (1.2)	-	2 (0.8)
Rash	0	1 (0.1)	0	3 (0.3)	0	0	1 (0.9)	1 (0.1)	-	-	-	0
Urticaria	0	0	0	3 (0.3)	-	-	-	0	-	-	-	0
Lip swelling	0	0	0	3 (0.3)	-	-	-	0	-	-	-	0
Cardiomyopathy	0	1 (0.1)	1 (0.5)	2 (0.2)	-	-	-	0	-	-	-	0
Vomiting	0	1 (0.1)	1 (0.5)	2 (0.2)	-	-	-	0	-	-	-	0
Adverse drug reaction	0	0	0	2 (0.2)	-	-	-	0	-	-	-	0
Oedema peripheral	0	0	0	2 (0.2)	-	-	-	0	-	-	-	0

PTs are presented in descending order of frequency according to the Pool Y1 All column. Blood intake categories: < 7 mL pRBCs/kg/month (low blood intake), 7 to 14 mL pRBCs/kg/month (moderate blood intake), and >14 mL pRBCs/kg/month (high blood intake).
Frequency is the number of patients with AE onset within the given year. N is the number of patients receiving deferasirox at the start of the given year.
A patient with multiple occurrences of an AE is counted only once in that AE category.

Post marketing experience

- Post-marketing experience

Deferasirox is commercially available within the United States, European Union, Switzerland, and other markets worldwide for the treatment of transfusional iron overload.

Safety data from all sources (literature, studies, spontaneous reporting) are reviewed on an ongoing basis for any impact on the EU SPC and local labelling.

The total cumulative patient exposure since the International Birth Date of 02-Nov-2005 up to 31-Oct-2010 was 89,168 patient-treatment-years. The total cumulative exposure in MAH sponsored investigational clinical trials (excluding PMS studies, third party study studies and registries) as of 31-Oct-2010 was 6,922 patients.

2.5.1. Discussion on clinical safety

As discussed with respect to efficacy results, the studies included in these analyses are heterogeneous. The proposed meta-analysis compared 2 populations with very different size which is a limitation of the proposed approach especially for safety. Infrequently transfused patients constitute a relatively small fraction of the subjects (15%). Data available for infrequently transfused paediatric patients was also too scarce to draw any firm conclusion on the safety in this subpopulation.

Therefore, due to heterogeneity of studies, results of this meta-analysis should be taken with caution and no firm conclusions can be drawn, particularly when looking at the data in subgroups by age.

Concerning the currently approved restricted indication, overall no new signal emerged from these studies. The overall adverse event profile was consistent with the known safety profile of Exjade and complications of underlying conditions. Despite the methodological pitfalls, the meta-analysis provided the best available estimate of the effect of Exjade on creatinine clearance relevant for the currently approved restricted indication. As this has been previously missing from the SmPC, a description of the magnitude of the effect on estimated renal clearance has been included in section 4.8 of the SmPC.

2.5.2. Conclusions on clinical safety

The safety data available based on the retrospective meta-analysis for infrequently transfused patients are not sufficient to draw any firm conclusion on the safety of deferasirox outside the currently approved restricted indication ("when deferoxamine therapy is contraindicated or inadequate"). Further to the assessment of the CHMP and their conclusions as detailed in this report that this extension of the indication was not considered approvable, the MAH decided not to pursue with the proposed change to the indication.

Concerning the currently approved restricted indication, the CHMP included a description of the magnitude of the effect on estimated renal clearance in section 4.8 of the SmPC based on the retrospective meta-analysis.

2.5.3. PSUR cycle

The Annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

No updates to the current version of the risk management plan are necessary.

2.7. Update of the Product information

Further to data submitted in this application, the following information was added to the summary of the safety profile in section 4.8 of the SmPC:

"In a retrospective meta-analysis of 2,102 adult and paediatric beta-thalassaemia patients with transfusional iron overload (including patients with different characteristics such as transfusion intensity, posology and treatment duration) treated in two randomised clinical trials and four open label studies of up to five years' duration, a mean creatinine clearance decrease of 13.2% in adult patients (95%CI: -14.4% to -12.1%; n=935) and 9.9% (95%CI: -11.1% to -8.6%; n=1142) in paediatric patients was observed during the first year of treatment. In a subset of patients followed for more than one year (n=250 up to five years), no further decrease in mean creatinine clearance levels was observed in subsequent years."

Changes were also made to the PI to bring it in line with the current Agency/QRD template (version 8.3), which were reviewed and accepted by the CHMP.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Exjade is an efficient oral iron chelator. An iron chelating agent permits to achieve safe levels of body iron. This is a slow process because only a small proportion of body iron is available for chelation at any moment.

The purpose of this submission was the extension of indication of deferasirox to first line use in infrequently transfused beta-thalassemia patients aged 6 years or older. Current standard therapy in this indication is subcutaneous deferoxamine.

The MAH submitted pooled analysis of six studies in infrequently transfused patients as well as a retrospective analysis of the data obtained in the pivotal study A 0107 providing comparative results of DFX versus DFO in order to demonstrate efficacy and safety of deferasirox in this population. Efficacy was assessed by mean changes in serum ferritin levels, liver iron concentration (LIC) and iron excretion (IE). Overall, the data submitted had many limitations and no conclusions could be drawn based on these results.

Uncertainty in the knowledge about the beneficial effects

The benefits of deferasirox as first-line treatment in infrequently-transfused patients beta outside the currently approved restricted indication (“when deferoxamine therapy is contraindicated or inadequate”) have not been established.

Risks

Unfavourable effects

No new signal emerged from these analyses: The overall adverse event profile was consistent with the known safety profile of Exjade and complications of underlying conditions.

Nephrotoxicity is a known safety concern with Exjade. The main related event observed more frequently in infrequently transfused patient was blood creatinine increased in the 1st year of treatment in 2 datasets. In a subset of patients followed for more than one year (n=250 up to five years), no further decrease in mean creatinine clearance levels was observed in subsequent years.

Uncertainty in the knowledge about the unfavourable effects

The data available for infrequently transfused paediatric were insufficient to draw any firm conclusion on the safety of deferasirox as first-line treatment in infrequently-transfused patients beta outside the currently approved restricted indication (“when deferoxamine therapy is contraindicated or inadequate”).

Benefit-Risk Balance

Importance of favourable and unfavourable effects and benefit-risk balance

Non-comparative results from the pooled analysis are difficult to interpret and are not sufficiently robust to draw conclusions. Retrospective analysis from the study A0107 also presented major methodological weaknesses which cannot allow to conclude on the efficacy profile of deferasirox versus deferoxamine in infrequently-transfused patients.

No new signal emerged from these analyses. However, in view of the lack of representativeness of the dataset, adverse events of interest and safety concern may not have occurred or be underestimated in the proposed analysis particularly the know concern of nephrotoxicity which requires close monitoring.

In the absence of established favourable and unfavourable effects, the benefit-risk balance of deferasirox as first-line treatment in infrequently-transfused patients beta outside the currently approved restricted indication ("when deferoxamine therapy is contraindicated or inadequate") cannot be considered as positive.

Discussion on the Benefit-Risk Balance

The CHMP agreed to include in section 4.8 of the SmPC a description of the magnitude of the effect on estimated renal clearance based on the retrospective meta-analysis.

4. Recommendations

Further to the assessment of the CHMP and their conclusions as detailed in this report that this extension of the indication was not considered approvable, the MAH decided not to pursue with the proposed change to the indication.

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Update of section 4.8 of the SmPC to include a description of the magnitude of the effect on estimated renal clearance based on a retrospective meta-analysis of 2,102 beta-thalassemia major patients exposed to deferasirox in 6 completed clinical trials. The Marketing Authorisation Holder also took the opportunity to update the product information with version 8.3 of the QRD template.

The requested variation proposed amendments to the SmPC and Annex II.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/216/2011 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.