NOVARTIS

Oncology Global Drug Development

EXJADE® (deferasirox)

CICL670E2422

Non-Interventional Study Final Report

REDACTED REPORT BODY

An observational, multi-center study to evaluate the safety of deferasirox in the treatment of pediatric patients with non-transfusion-dependent iron overload

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Research question and objectives	The purpose of this observational study was to provide further assessment of the safety of deferasirox in NTDT pediatric patients with documented iron overload as defined in local product label.
	• Primary objective: To characterize the long-term safety profile of deferasirox in pediatric patients with NTDT with exposure up to 5 years
	• Secondary objectives:
	  • To evaluate the incidence of serum creatinine and SGPT (ALT) increases in actual practice setting
	  • To evaluate renal and hepatic safety parameters over time
	  • To evaluate growth by gender
	  • To evaluate sexual development by gender
	  • To evaluate long term efficacy of deferasirox as measured by serum ferritin and LIC
	  • To evaluate all other safety parameters (ECG, vital signs, audiometry and ophthalmology examinations)

Countries of study	Thailand, United Arab Emirates, Saudi Arabia, Lebanon, France, United States of America, Egypt, Oman, Turkey.
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Table of contents

List of tables

List of figures

1 Abstract

Title

An observational, multi-center study to evaluate the safety of deferasirox in the treatment of pediatric patients with non-transfusion-dependent iron overload

Version and date

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Name and affiliation of main authors

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Keywords

Non-transfusion-dependent thalassemia (NTDT), EXJADE (deferasirox), dispersible Tablets (DT), film coated tablets (FCT), pediatric patients

Rationale and background

The purpose of this observational study was to provide further assessment of the safety of deferasirox in NTDT pediatric patients with documented iron overload as defined in the local product label. The four-year extension of the phase III trial, Study CICL670A0107E, found that deferasirox did not impair growth in pediatric patients with β-thalassemia major and transfusional iron overload. However, this effect has not been studied in NTDT pediatric patients and requires further confirmation. Thus, in NTDT population, growth and the sexual development of children between age ≥ 10 to <18 were assessed in the present study.

Research question and objectives

This observational study evaluated the long-term safety of deferasirox therapy in pediatric patients ≥ 10 to <18 years with NTDT in actual practice setting.

The primary objective of this study was to characterize the long-term safety profile of deferasirox in pediatric patients with NTDT with exposure up to 5 years.

Study design

This study was non-interventional and did not impose a therapy protocol, diagnostic/therapeutic interventions or a visit schedule. However, a minimum of quarterly visits were suggested. Patients were treated with deferasirox in accordance with the local (country-specific) deferasirox prescribing information. In the study deferasirox was given as deferasirox DTs or FCTs. DTs were used in 3 dosing strengths (125, 250, 500 mg) and was dosed based on body weight with initial recommended dose of 10 mg/kg/day. FCTs were available in 3 dose strengths (90 mg, 180 mg, and 360 mg) and was dosed based on body weight with initial recommended dose of 7 mg/kg/day. The study mandated stopping rules for deferasirox treatment based on serum ferritin (SF) and/or LIC levels as a recommendation to investigators and based on deferasirox prescribing information. In the study, patients are treated based on investigator judgement following local practices.

Pediatric patients aged ≥ 10 to <18 years at enrollment with NTDT and treated with deferasirox were followed for up to 5 years from the start of deferasirox treatment. Retrospective data collection was conducted for patients who have started deferasirox 12 months or less prior to enrollment. The baseline was defined as the timeframe before the patient starts treatment with deferasirox. In patients who had

protocol specified assessments performed prior to the date of first deferasirox treatment, the baseline data was collected if it was within the following timeframe prior to the date of starting deferasirox treatment:

- 1.5 months for all laboratory assessments
- 6 months for vital signs, weight, height, LIC, ECG, ECHO, CMR, ocular and audiometry assessments
- 12 months for pubertal assessments (Tanner stage).

Post baseline data were collected from the start date of deferasirox treatment and then on for up to 5 years.

Setting

Pediatric patients aged ≥ 10 to <18 years at enrollment with NTDT treated with deferasirox.

The study enrolled patients planned to be treated with deferasirox and patients who started deferasirox treatment ≤ 12 months prior to enrollment.

Subjects and study size

Number of patients planned were a minimum of 40 and the actual number of patients enrolled were 45.

A minimum of 20 patients were initially planned for enrollment in each of the 2 age categories (10 to ≤12 years and >12 to <18 years). The actual enrollment numbers were 21 patients in the 10 to ≤12 years category and 24 patients in the >12 to <18 years category.

Variables and data sources

The study was based on primary data collection directly from healthcare professionals and the variables are listed below:

- serum creatinine, creatinine clearance, serum ferritin, urea, SGOT (AST), SGPT (ALT), alkaline phosphatase, bilirubin and proteinuria,
- LIC, CMR, echocardiography, ECG, vital signs,
- cardiac events potentially related to cardiac iron overload,
- height, weight
- sexual development according to Tanner stage (ages ≥10 and <18 years)
- audiometry and ophthalmology examination findings,
- transfusion requirements,
- concomitant medication at time of renal or hepatic AEs,
- adverse events (AEs)

Statistical methods

All data summaries and analyses were descriptive only. Categorical data (e.g., gender, race, etc.) were summarized by means of contingency tables; a “missing” category was included as applicable. Percentages were calculated using the number of patients in the relevant population or subgroup as the denominator. Quantitative data (e.g., age, body weight, etc.) was summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum and maximum).

Results

- Overall, 45 patients were enrolled; 26 patients (57.8%) completed the treatment as per protocol and 19 patients (42.2%) discontinued the study. Twenty-one patients were treated with deferasirox DT formulation only, 15 patients switched from DT to FCT, and 9 patients were treated with deferasirox FCT formulation only. The median exposure to deferasirox (regardless of formulation) was 37.52 months (range: 3.2 to 68.7 months). Nineteen patients overall were treated for ≥ 48 months.

- Serum ferritin baseline information was available in 33 (73.3%) patients and LIC baseline information was available in 18 (40.0%) patients, the median values for LIC and SF at baseline were 8.3 mg Fe/g dw liver (Min-Max: 2.70-23.20), and 801.0 µg/L (Min-Max: 201-2713), respectively.
- Overall, 35(77.8%) patients reported AEs, the most common AEs by PT were upper respiratory tract infection in 9 (20.0%) patients, thrombocytosis, pyrexia, cough, rhinitis, and Vitamin D deficiency in 4 (8.9%) patients each. No patients discontinued the study drug due to AEs.
- Overall, SAEs regardless of study drug relationship were reported in 5 (11.1%) patients which included SAEs by PT of gastroenteritis in 2 (4.4%) patients, portal vein thrombosis, post procedural haemorrhage, influenza and vomiting, in 1 (2.2%) patient each. Vomiting was the only SAE suspected to be study drug related, reported in 1 (2.2%) patient.
- Overall, 9 (20.0%) patients reported AESIs and none of them were study drug related. Hepatic and renal AESIs regardless of study drug relationship, with moderate severity, were reported in 1 patient (2.2%), which included increased ALT and increased blood creatinine. Both events resolved with no action taken to deferasirox treatment.
- ALT, AST and total bilirubin baseline information was available in 37 (82.2%) patients, 35 (77.8%) patients, and 31(68.9%) patients, respectively. No patient in the study had an episode of ALT >5×ULN in at least 2 consecutive post-baseline measurements at least 7 days apart. Despite some missing assessments, no clinically concerning elevations of hepatic enzymes were observed. Most post-baseline values stayed the same or improved.
- One case met Hy's Law criteria but was not considered a DILI case due to confounding factors including medical history of mild hepatic siderosis, infection of Epstein-Barr virus, abnormal liver function assessments at baseline, moderate cholelithiasis 1 day before the biochemical Hy's Law criteria were met.
- Serum creatinine baseline information was available in 37 (82.2%) patients, and CrCl baseline information was available in 27 (60.0%) patients. No concerning decreases in renal function was observed based on SCr and CrCl monitoring. No patient had a notable range (defined as two consecutive values >ULN and >33% increase from baseline) in SCr. No patients met the criteria for notable decreases in CrCl.
- Overall, an increase in weight, height, and BMI from baseline to Quarter 20, was observed. Shift tables on height, weight and BMI SDS showed that majority of patients remained in the same SDS category as at baseline (low or normal). The individual growth curves showed continuous growth in male and female pediatric patients from both age cohorts (10-<=12 and >12-<18) during deferasirox treatment, although growth trends lie within the lower percentiles of US Clinical Growth Charts. These results and conclusions of this study are in line with what was observed when the same analysis was conducted in historical Study CICL670A0107E.
- Limited patient data was available for Tanner stage analyses, with most patients having only 1 to 3 values. Eleven patients had both baseline and post-baseline assessments. One patient exhibited a clinically significant abnormality (delayed puberty) before starting treatment, which persisted throughout the study.
- The long-term efficacy of deferasirox was measured by SF and LIC among 45 patients. The results showed that 19 (42.2%) patients achieved SF levels below 300 µg/L, and 15 (33.3%) patients achieved LIC levels below 3 mg Fe/g dw liver. Additionally, 4 (8.9%) patients restarted deferasirox treatment after temporary interruption due to SF levels below 300 µg/L or LIC levels below 3 mg Fe/g dw liver.
- Abnormal hematology values were noted in some patients, with most having high or low values prior to treatment or at baseline. Post-baseline, low neutrophils were reported in 9 patients and low platelets in 3 patients.

- Audiometric assessments were documented for 24 patients. Most had post-baseline assessments only. One patient had a clinically significant abnormality (hypoacusis) that was mild and not related to the study treatment. This patient continued treatment until discontinuation due to lack of MRI confirmation of iron overload.
- Ophthalmological examinations were documented for 20 patients. Most had post-baseline assessments only. One patient had a clinically significant ocular abnormality (myopia) prior to treatment, with no post-baseline assessment or ocular AEs reported.
- The results of echocardiograms, ECGs, and vital signs showed no significant abnormalities with the limited data collected.

Discussion

The study enrolled 45 patients, with 26 (57.8%) patients completing the treatment as per protocol and 19 (42.2%) patients discontinuing the study. Patients were treated with different formulations of deferasirox, with some switching from DT to FCT during the study.

AEs were reported by 35 (77.8%) patients, with infections and infestations being the most common. Study drug-related AEs were minimal (including abdominal pain upper in 2 (4.4%) patients; dermatitis allergic, vomiting, dizziness gastritis, and hyperchlorhydria in 1 (2.2%) patient each), and no patients discontinued the study drug due to AEs. SAEs were reported in 5 (11.1%) patients, with one (2.2%) SAE of vomiting, suspected to be study drug-related. Hepatic and renal AESIs were reported in 1 (2.2%) patient, both of which resolved without altering deferasirox treatment.

No patients experienced clinically concerning elevations of hepatic enzymes, and renal function remained stable throughout the study. Growth and development were evaluated over five year period. Increases in weight, height, and BMI were observed over five years. Patients aged 12 to 18 showed improvements in height SDS.

Limited data on Tanner stage analyses indicated that most patients had few assessments, thus with one patient experiencing delayed puberty throughout the study.

The long-term efficacy of deferasirox showed a decreasing trend in SF and LIC, and approximately up to half of patients reaching target levels of SF or LIC post-baseline

Audiometric and ophthalmological assessments showed minimal clinically significant abnormalities, with one patient experiencing mild hypoacusis and another with pre-existing myopia.

No unexpected safety finding were reported.

Conclusion

Overall, the treatment was well-tolerated. The AEs observed in this study are the expected AEs in the patient population. Few study drug-related AEs were reported., positive growth and development outcomes were observed over the long term. The study highlighted stable renal function and no clinically concerning elevations of hepatic enzymes, reinforcing the overall positive impact of deferasirox treatment. No new safety signals were identified, and the long-term efficacy and safety of deferasirox remains consistent with its established benefit/risk profile.

Marketing Authorization Holder(s)

Novartis Europharm Ltd

Name(s) and Affiliation(s) of Principal Investigator(s)

[redacted]

2 List of abbreviations

AE	Adverse Event
AESI	Adverse events of special interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body mass index
CMR	Cardiac magnetic resonance
CrCl	Creatinine Clearance
DFX	Deferasirox
DILI	Drug induced liver injury
DT	Dispersible Tablet
ECG	Electrocardiogram
ECHO	Echocardiogram
EMA	European Medicines Agency
EOS	End of study
FAS	Full Analysis Set
FCT	Film Coated Tablet
FDA	Food and Drug Administration
HbE	Hemoglobin E
HbH	Hemoglobin H
LIC	Liver iron concentration
MAH	Marketing Authorisation Holder
MRI	Magnetic resonance imaging
NIS	Non-interventional study
NTDT	Non-Transfusion-Dependent Thalassemia
PASS	Post authorization safety study
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred term
SAE	Serious Adverse Event
SCr	Serum Creatinine
SDS	Standard deviation scores
SF	Serum ferritin
ULN	Upper Limit of Normal
WHO-UMC	World Health Organization–Uppsala Monitoring Centre

3 Investigators

The names and details of all the Investigators for each country in which the study was performed are included in Appendix 16.1.4.

4 Other responsible parties

[redacted] was the other party responsible for data management support, quality control, database lock timelines and management.

[redacted] contact details:

[redacted]

5 Milestones

Study milestones are summarized in Table 5-1.

Table 5-1 Study milestones

Milestone	Planned date	Actual date
Start of data collection	16 Apr 2014	13 Aug 2014
End of data collection (Last date of data collection)	30 Jul 2025	08 Jan 2025
Registration in the EU PAS register	30 Nov 2013	30 Nov 2013
Annual Safety Report 1	31 Dec 2014	19 Dec 2014
Annual Safety Report 2	31 Dec 2015	04 Dec 2015
Annual Safety Report 3	31 Dec 2016	05 Dec 2016
Annual Safety Report 4	31 Dec 2017	16 Nov 2017
Annual Safety Report 5	31 Dec 2018	09 Nov 2018
Annual Safety Report 6	31 Dec 2019	12 Nov 2019
Annual Safety Report 7	31 Dec 2020	10 Dec 2020
Annual Safety Report 8	31 Dec 2021	16 Nov 2021
Annual Safety Report 9	31 Dec 2022	16 Nov 2022
Annual Safety Report 10	31 Dec 2023	29 Nov 2023
Final Study Report	28 Apr 2025	05 Jun 2025

6 Rationale and background

Non-transfusion-dependent thalassemia (NTDT) is a broad spectrum of different forms of thalassemia which include β-thalassemia intermedia, hemoglobin E (HbE) β-thalassemia, and hemoglobin H (HbH) disease α-thalassemia. The combination of ineffective erythropoiesis, anemia, and hypoxia leads to a compensatory increase in serum levels of erythropoietin (EPO), as well as a decrease in serum levels of hepcidin, which promotes an increase in intestinal iron

absorption and an increased release of recycled iron from the reticuloendothelial system (Rivella 2012). This in turn results in depletion of macrophage iron, relatively lower levels of serum ferritin, and increased liver iron concentration (Origa et al 2007) with subsequent release into the circulation of labile plasma iron and non-transferrin-bound iron which can cause target-organ damage (Taher et al 2009). In addition to iron overload due to increased interstitial iron absorption, these patients may also accumulate iron from occasional or more frequent transfusions (Musallam et al 2012).

An analysis from clinical data on 378 patients with hemoglobin E β-thalassemia showed that 75% of NTDT patients had growth retardation and some patients presented with delay in sexual development (Fucharoen and Winichagoon 2000). The mechanism of short stature in these patients seems to be complex and has been attributed to growth hormone (GH) deficiency, hypothyroidism, diabetes mellitus, zinc deficiency, and low hemoglobin levels. Iron load was also stated as the main contributor to hypothalamic-pituitary-gonadal (H-P-G) dysfunction and GH dysfunction in many patients with thalassemia (Borgna-Pignatti et al 1985).

Serum ferritin (SF) has been traditionally used to assess transfusional iron overload with a well-established correlation to liver iron concentration (LIC), a more direct measurement of liver tissue iron. However, SF levels have recently been reported to underestimate LIC in patients with NTDT as compared to regularly transfused patients (Origa et al 2007; Pakbaz et al 2007).

NTDT patients whose LIC levels are ≥ 5 mg Fe/g dry weight (dw) (or serum ferritin level >800 ng/mL) are at higher risk of developing iron-related morbidity (Musallam et al 2013; Weatherall 2012). The use of iron chelation therapy in NTDT has been documented in previous reports and small uncontrolled studies (Olivieri et al 1992; Taher et al 2010) and is recommended by Thalassemia International Federation (Taher et al 2013).

Out of three available chelators, deferasirox is the only drug that has been evaluated in a randomized clinical study in patients with NTDT (CICL670E2209, the THALASSA study). In this study, deferasirox compared with placebo, at starting doses of 5 and 10 mg/kg/day with dose escalations up to 20 mg/kg/day in patients with high levels of iron overload (LIC ≥ 5 mg Fe/g dw and SF > 300 ng/mL) significantly reduced LIC and SF levels after one year of treatment. Based on the results of this study, deferasirox was approved by FDA and in the EU for the treatment of iron overload in this population (Taher et al 2012).

Both adults and pediatric population (21 patients) under 18 years were included in the efficacy and safety analysis of the THALASSA study. Diarrhea, rash, and nausea were the most frequent study drug-related AEs. Both diarrhea and rash were more frequent in the 10 mg/kg/day deferasirox group than in the 5 mg/kg/day deferasirox group or the placebo groups, but no difference between groups was observed for nausea. There were no deaths, and the incidence of SAEs was comparable between treatment groups. Eight patients experienced AEs resulting in study discontinuation (Taher et al 2012). Renal function, assessed by measuring serum creatinine, creatinine clearance, and Urinary Protein Creatinine Ratio (UPCR), was only mildly affected by deferasirox, which was reflected by a small number of patients developing abnormal values that resolved spontaneously or after drug interruption (further details on the THALASSA study are provided in Appendix 16.1.1-Protocol-Section 5).

The effect of deferasirox on growth and development was studied in the four-year extension of the phase III trial, Study CICL670A0107E, in pediatric patients with β-thalassemia major and transfusional iron overload (Cappellini et al 2011). Height, weight, growth, and pubertal stage (female breast development, male testes volume, and pubic hair) were analyzed annually. The study results indicated that growth and sexual development were not impaired and progressed normally during long-term deferasirox treatment, thus suggesting that iron chelation with deferasirox abates the inhibitory effects of iron overload. However, this positive effect of deferasirox has not been studied in NTDT pediatric patients and therefore requires confirmation.

Because of the chronic nature of chelation therapy and the importance of patient compliance, an improved deferasirox formulation for oral administration has been developed. The film coated tablet (FCT) used in this study had the same active substance but was strength-adjusted to achieve comparable exposure to the dispersible tablet formulation.

The study CICL670E2422 (hereafter referred to as E2422) represents a key component of the active surveillance program for deferasirox. The purpose of this observational study was to provide further data, in addition to that obtained from the THALASSA trial, for the assessment of the safety of deferasirox in NTDT pediatric patients with documented iron overload as defined in a local product label. In addition, growth and sexual development of children between age ≥ 10 to < 18 was assessed.

7 Research question and objectives

This observational study evaluated the long-term safety of deferasirox therapy in pediatric patients ≥ 10 to < 18 years at enrollment with NTDT in actual practice setting.

Objectives	Endpoints
Primary Objective	
To evaluate the long term safety of deferasirox	Proportion of patients having SAEs that were considered to be related to study drug up to 5 years from the start of deferasirox treatment.
Secondary Objectives	
To evaluate the incidence of serum creatinine and SGPT (ALT) increases in actual practice setting	The proportion of patients having (up to 5 years from the start of deferasirox treatment): Serum creatinine > 33% above baseline and above the age adjusted ULN in at least two consecutive post-baseline measurements at least 7 days apart from each other. SGPT (ALT) above 5 × ULN in at least two consecutive post-baseline measurements at least 7 days apart from each other
To evaluate renal and hepatic safety parameters over time	Absolute/relative changes from baseline of SGPT (ALT), SGOT (AST), total bilirubin, alkaline phosphatase, serum creatinine, creatinine clearance quarterly up to 5 years. Proportion of patients having hepatic and renal clinical events that are considered to be related to study drug up to 5 years from the start of deferasirox.
To evaluate growth by gender	Absolute change in BMI, weight and height from baseline to EOS Proportion of patients falling behind in growth based on height, weight and BMI
To evaluate sexual development by gender	Mean age at assessment for each Tanner stage Changes from baseline to the last on-study value of all Tanner stage parameters.
To evaluate long term efficacy of deferasirox as measured by serum ferritin and LIC	Absolute/relative change in SF and LIC from baseline to EOS Proportion of patients achieving a SF < 300 ng/mL Proportion of patients achieving LIC < 3 mg Fe/g dw Proportion of patients reinitiating deferasirox after discontinuation due to a "stopping rule" *
To evaluate all other safety parameters	Significant findings of safety data (ECG, vital signs, audiometry and ophthalmology examinations) were documented as adverse events.

*Stopping rule: it was recommended that treatment was stopped once a satisfactory body iron level has been achieved (LIC < 3 mg Fe/g dw or serum ferritin < 300 ng/mL).

Source: Appendix 16.1.1-Protocol-Table 6-1

8 Amendments and updates to the protocol

The protocol amendments are summarized in Table 8-1.

Table 8-1 Study protocol amendments and updates

S.No	Date	Amendment or update
1	28 Jan 2014	Amendment 1 This amendment was undertaken in response to PRAC request with an objective to evaluate renal and hepatic safety parameters over time, sexual development by gender, safety parameters, serum creatinine were revised. Additional text was added on “physician selection”, “population”, “protocols for observational studies”, “handling of missing values”, “supportive analyses”, and “criteria for clinically notable and extended laboratory ranges”.
2	14 Oct 2014	Amendment 2 This amendment was undertaken in response to PRAC request. Annual ‘Safety’ reports were changed to state ‘Interim’ reports. The changes implemented in this protocol amendment included revision of text on “physician selection”, “population” and “Inclusion/Exclusion criteria”.
3	06 Jul 2015	Amendment 3 The Amendment was undertaken as a result of the development of a deferasirox film-coated tablet for oral administration and to allow the inclusion of patients who were prescribed the film-coated tablet formulation. In addition, strength and dosing of the new formulation was explained.
4	01 Dec 2015	Amendment 3.1 Request from EMA that MAH removes all tradename “Jadenu” in the protocol. Throughout the protocol, Jadenu was deleted and replaced with Deferasirox FCT. Throughout the protocol, Exjade was deleted and replaced with Deferasirox DT
5	10-Jun-2020	Amendment 4 Amendment 4 was undertaken to implement a timeframe around the baseline data collection, to clarify what was considered as post-baseline safety assessment for inclusion in the safety set, to clarify the stopping rules in the context of a non-interventional study, to clarify the recommendation of monthly monitoring of serum ferritin to avoid overchelation, and to report as adverse events when it occurs, and to modify the lower age group and the subgroup categories for sexual and growth analysis. An editorial update of sensitivity analyses to supplementary analyses and clarification on when the analysis would be performed.

Source: Appendix 16.1.1-Protocol-Table 3-1 and Section 3

9 Research methods

9.1 Study design

This study was non-interventional and did not impose a therapy protocol, diagnostic/therapeutic interventions or a visit schedule. However, a minimum of quarterly visits were suggested. Patients were treated with deferasirox in accordance with the local (country-specific) deferasirox prescribing information.

The study included stopping rule for deferasirox treatment based on SF and/or LIC levels as a recommendation to investigators and based on deferasirox prescribing information. In the study, patients were treated based on investigator judgement following local practices. The study took place in actual practice setting and monitored patients treated with deferasirox according to the local (country-specific) prescribing information. The study was based on primary data collection directly from healthcare professionals. Retrospective data collection (through interviews and questionnaires) was done for patients who had started deferasirox 12 months or less prior to enrollment.

The enrollment was defined as the patient's entry into the study, which was the point at which informed consent form was signed. Data were collected on a minimum of 40 eligible pediatric patients who signed informed consent. These patients aged ≥ 10 to < 18 years at enrollment, were diagnosed with NTDT and required to be treated with deferasirox or started deferasirox treatment 12 months or less prior to enrollment. These patients were followed for up to 5 years from the start of deferasirox treatment. The baseline was defined as the timeframe before the patient started treatment with deferasirox (Appendix 16.1.1-Protocol-Section 7.1).

9.1.1 Investigational treatment

Deferasirox dispersible tablets (DTs)

Deferasirox dispersible tablet was used in 3 dosing strengths (125, 250, 500 mg) and was dosed based on body weight with initial recommended dose of 10 mg/kg/day (Table 9-1).

It was recommended that deferasirox was taken on an empty stomach, at least 30 minutes prior to food intake preferably at the same time every day. The tablets were dispersed by stirring in a glass of water or apple or orange juice (100 to 200 mL) until a fine suspension was obtained. After the suspension has been swallowed, any residue was re-suspended in a small volume of water or juice and swallowed. The tablets were not chewed or swallowed whole. Dispersion in carbonated drinks or milk was not recommended due to foaming and slow dispersion, respectively.

Deferasirox Film Coated Tablets (FCTs)

Because of the chronic nature of chelation therapy and the importance of patient compliance, an improved deferasirox formulation for oral administration has been developed.

It contains the same active substance but was strength-adjusted to achieve comparable exposure to the dispersible tablet. FCTs are available in 3 dose strengths (90 mg, 180 mg, and 360 mg) and are dosed based on body weight with initial recommended dose of 7

mg/kg/day (Table 9-1). The FCT can be taken with or after a light meal, preferably at the same time every day. For patients who are unable to swallow whole tablets, FCT may be crushed and administered by sprinkling the full dose onto soft food, e.g. yogurt or apple sauce (pureed apple).

Dose adjustments were based on LIC and/or serum ferritin levels, safety and tolerability as defined by local label requirements and the investigator's judgement. In general, it was recommended that treatment should be stopped once a satisfactory body iron level had had achieved (LIC < 3 mg Fe/g dw or serum ferritin < 300 ng/mL). In the context of this noninterventional trial where no therapy protocol was imposed and patients were treated based on investigator judgment following local practice, investigators were advised to follow the stopping rules described above, and reintroduction of deferasirox therapy could take place if the LIC and/or SF levels increased above the thresholds as per local label requirements.

Patients were allowed to change deferasirox formulation under the advice and guidance of the Investigator.

For further details on treatment administration refer to Appendix 16.1.1-Protocol-Section 7.1.

Table 9-1 Dose conversion between dispersible tablets and film coated tablets

Deferasirox dispersible tablets	Deferasirox film-coated tablets
Dose range:	**Dose range:**
10-40 mg/kg/d; calculated and rounded to the nearest whole tablet size.	7-28 mg/kg/d; calculated and rounded to the nearest whole tablet size.
Dose adjustment:	**Dose adjustment:**
Increments of 5-10 mg/kg/d	Increments of 3.5-7 mg/kg/d
Deferasirox DT therapeutic dose range:	**Deferasirox FCT therapeutic dose range:**
10 mg/kg/d	7 mg/kg/d
20 mg/kg/d	14 mg/kg/d
30 mg/kg/d	21 mg/kg/d
40 mg/kg/d (max. recommended dose)	28 mg/kg/d (max. recommended dose)

Source: Appendix 16.1.1-Protocol-Table 7-1

Treatment duration

Since the study was non-interventional, deferasirox treatment duration was at the discretion of the physician and in accordance with the local country-specific deferasirox prescribing information. The maximum duration of deferasirox treatment observed was for 5 years.

9.1.2 Definition of End of Study

The study ended when each of the patient enrolled in the study was either withdrawn from the study or completed 5 years from the start of deferasirox treatment, whichever occurred earlier.

9.2 Setting

This study was carried out with specialist hematologists, internists, pediatricians or physicians working at specialized thalassemia centers, with a pediatric NTDT patient population and an interest in participating in such an observational study. These physicians were identified after detailed site selection visits at thalassemia centers located in countries with high prevalence of thalassemia. All sites had previously participated in thalassemia clinical research programs and had sufficient experience in treatment of these patients.

Prior to study site selection, Novartis representatives reviewed the protocol with potential physicians at the center and an informed decision was taken by the physician whether or not to participate.

9.3 Patients

A minimum of 40 patients who were previously treated (maximum of 12 months) or were planned to be treated with deferasirox, were enrolled in this registry. At least 20 patients each were planned to be enrolled for the two age categories (10 to ≤ 12 years and > 12 to < 18 years).

Patients were enrolled if they met the following criteria.

Inclusion criteria:

Patients eligible for inclusion in this study met all of the following criteria:

1. Male or female aged ≥ 10 but < 18 years old with non-transfusion-dependent thalassemia syndromes inclusive of beta-thalassemia intermedia, HbE beta-thalassemia or alpha thalassemia intermedia (HbH disease) and chronic iron overload

   AND

2. Patients currently treated for a maximum of 12 months or patients planned to be treated with deferasirox

   AND

3. Written informed consent obtained prior to any screening procedures. The consent form was signed by the patient's legal guardian.

Exclusion Criteria

1. Patients treated with deferasirox in an interventional clinical study.

9.4 Variables

For details on variables assessed and frequency of assessment refer to Appendix 16.1.1-Protocol-Table 7-2.

Patient demographics and other baseline characteristics

The following baseline information was collected (when available):

- Date of birth, gender, race, and ethnicity
- Medical history and disease characteristics
- History of previous iron chelation
- History of transfusion in the 12 months prior to the start of deferasirox treatment
- Baseline laboratory assessments such as serum creatinine (SrCr), creatinine clearance, SF, urea, SGOT (AST), SGPT (ALT), alkaline phosphatase, bilirubin and proteinuria.
- Baseline vital signs, weight, height, sexual development assessment, ECG, echocardiography, cardiac magnetic resonance (CMR), and LIC.

For patients already treated with deferasirox, transfusion, concomitant medications and concomitant diseases were collected at enrollment.

Safety

Patient safety was monitored by reviewing medical and laboratory records and collecting available data on:

- SrCr, creatinine clearance, SF, urea, SGOT (AST), SGPT (ALT), alkaline phosphatase, bilirubin and proteinuria, LIC, CMR, echocardiography, ECG, vital signs,
- cardiac events potentially related to cardiac iron overload,
- height, weight, BMI,
- sexual development according to Tanner stage,
- audiometry and ophthalmology examination findings,
- concomitant medications
- adverse event (AE)

For details on AE collection and reporting, refer to Appendix 16.1.1-Protocol-Section 9.

9.5 Data sources and measurement

This study was retrospectively designed and the data was prospectively collected from health care providers of eligible patients at participating clinical sites. The baseline is defined as the time frame before the patient starts treatment with deferasirox.

In patients who have protocol specified assessments performed prior to the date of first deferasirox treatment, the baseline data was collected if it was within the following timeframe prior to the date of starting deferasirox treatment (also refer Appendix 16.1.1-Protocol-Table 7-2):

- 1.5 months for all laboratory assessments
- 6 months for vital signs, weight, height, LIC, ECG, ECHO, CMR, ocular and audiometry assessments
- 12 months for pubertal assessments (Tanner stage).

Post baseline data was collected from the start date of deferasirox and then up to 5 years.

Sites enrolling patients in this study recorded data on eCRFs provided by Novartis (or designee) which captured, checked, stored and analyzed the data.

CROs followed their own internal SOPs that were reviewed and approved by Novartis.

Concomitant or prior medications entered into the database were coded using the World Health Organization (WHO) Drug Reference List. Medical history/current medical conditions and adverse events were coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Safety data was transferred to Novartis at a frequency as defined in the protocol and/or CRO contract. Clinical data was transferred to Novartis after closure of the study. For patients who discontinue prematurely, the reason for discontinuation was determined.

9.6 Bias

Measures to address bias were not applicable in this study.

9.7 Study size

This was a non-interventional study which planned to enroll a minimum of 40 patients. No formal sample size calculation based on the primary endpoint of long-term safety was performed. For further details on study size selection refer to Appendix 16.1.1-Protocol-Section 7.5.

The table below (Table 9-2) shows that the sample size means that there was a reasonable chance to detect AEs occurring with an incidence of 5% or higher.

Table 9-2 Probability to observe at least one AE for different incidence rates

Incidence rate of an adverse event	Probability that at least one patient out of 40 experiences the adverse event
3%	0.70
4%	0.80
5%	0.87
6%	0.92
10%	0.99
15%	1.00

Source: Appendix 16.1.1-Protocol-Section 7.5

9.8 Data transformation

All data summarized and analyzed were descriptive only with no formal inferential testing. All analyses, summaries, figures and listings were performed on the complete pool of patients (represented by an “All patients” column).

Categorical data (e.g., gender, race, etc.) were summarized; a “missing” category were included as applicable. Percentages were calculated using the number of patients in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) were summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum and maximum).

9.9 Statistical methods

All analyses were performed by Novartis. SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA) was used to perform all data analyses and to generate tables, figures, and listings. For a detailed description of statistical methods, variable derivation and imputation rules, refer to Statistical Analysis Plan (SAP) (Appendix 16.1.9).

9.9.1 Analysis sets

The **Full Analysis Set** (FAS) comprises all patients who received at least one dose of deferasirox during the study.

The **Safety Set** includes all patients who received at least one dose of deferasirox during the study and have at least one post-baseline safety assessment. For post-baseline safety assessments, if a patient has any assessment taken a day after treatment start date for examination-based assessments, e.g. laboratory, the patient was included. For AE/ Death patients with an AE start date/ death date on or after the start date of treatment were considered as having as least one post-baseline safety assessment and were included in the Safety Set.

9.9.2 Main statistical methods

9.9.2.1 Analysis supporting primary objective

The primary objective was to evaluate the long-term safety of deferasirox as determined by adverse events. On-treatment events were considered, post-treated events (> 30 days post treatment discontinuation) were included in the listing.

Primary endpoint

The primary variable was the proportion of patients having SAEs that were considered related to study drug over the period of up to 5 years from the start of deferasirox treatment.

Statistical hypothesis, model, and method of analysis

Counts and frequencies of patients with any drug related SAEs were provided descriptively on Safety Set overall and by preferred term (PT) and system organ class (SOC). Analyses were performed overall and by first formulation received/first switch/second switch (see Appendix 16.1.9-SAP-Section 2.2.4)

9.9.2.2 Analysis supporting secondary objectives

Secondary endpoints

All secondary endpoints were analyzed using the on-treatment period, unless specified otherwise.

Incidence of serum creatinine and ALT/AST increases in actual practice setting

Counts and frequencies as well as 95% CI were provided on Safety Set for patients with:

- Serum creatinine > 33% above baseline and the age adjusted ULN (as per local normal ranges) in at least two consecutive post-baseline measurements at least 7 days apart from each other.
- ALT above 5 × ULN in at least two consecutive post-baseline measurements at least 7 days apart from each other.
- AST above 5 × ULN in at least two consecutive post-baseline measurements at least 7 days apart from each other.

Renal and hepatic safety parameters over time

Proportion of patients having AEs related to hepatic and renal functions that were considered to be related to study drug over the period up to 5 years from the start of deferasirox treatment were calculated (were presented in the overall suspected to be drug related AEs output).

For laboratory parameters directly related to hepatic parameters: ALT, AST, total bilirubin, alkaline phosphatase and directly related to renal parameters: serum creatinine, creatinine clearance; observed values (and changes from baseline) averaged at baseline, after first intake of study medication to day 30, day 31 to day 90 and per subsequent quarter were summarized by descriptive statistics (n, mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum).

Growth by gender

The time-course of weight, height and BMI and its absolute changes from baseline, as appropriate was summarized by gender on Safety Set using descriptive statistics.

All individual trajectories for weight, height and BMI were superimposed on a graph with CDC US growth chart percentiles (5th, 25th, 50th, 75th, 95th), available for patients from 10 to 20 years.

In addition, weight, height and BMI were flagged according to these percentile categories [0-5^{th}); [5^{th} - 25^{th}); [25^{th} - 50^{th}); [50^{th}- 75^{th}); [75^{th} - 100^{th}] and shift tables were provided to compare baseline to the last available value on study.

Summary statistics of the height, weight and BMI standard deviation scores (SDS) for baseline, end of each year as well as end of study and change from baseline by gender and age category at enrollment (10 - < =12, >12 - < 18) were provided. The same analysis mentioned above was also done for study ICL670A0107E for the same age category patients (i.e.,, 10 - <= 12, 12 - < 18) as E2422. ICL670A0107E was a registry study with the historical data from the four-year follow-up of the premarket clinical trial for children with β-thalassemia who are on a regular transfusion program. For further information on growth by gender calculation refer to Appendix 16.1.9-SAP-Section 2.7.1.3.

Sexual development by gender

Shift tables for Tanner stages to compare baseline to the last on-study (on-treatment or post-treatment) value were provided. Descriptive statistics were also provided for age at assessment for each Tanner stage.

Number and percentages of patients who were below, within and above the Marshal standards (Marshall and Tanner 1970) (mean age ± 2 SD) for each Tanner stages by gender were provided.

Delayed puberty in girls is defined as failure to attain Tanner Stage 2 (for both breast development and pubic hair) by age 13, or absence of menarche by age 15 or within 5 years of attainment of Tanner Stage 2. Delayed puberty in boys is defined as failure to attain Tanner Stage 2 (for both testis and pubic hair) by age 14. Delayed puberty was listed.

Long term efficacy of deferasirox as measured by serum ferritin and LIC

The time-course of serum ferritin (quarterly) and LIC (yearly) and its absolute changes from baseline were summarized on FAS using descriptive statistics.

Counts and frequencies were provided on FAS for patients:

- achieving a SF < 300 ng/mL at any time during study;
- achieving LIC < 3 mg Fe/g dw at any time during study;
- restarting deferasirox treatment after temporary interruption due to one of the two criteria mentioned above (SF < 300 ng/mL or LIC < 3 mg Fe/g dw at any time during study).

9.9.2.3 Safety analysis

9.9.2.3.1 Adverse events (AEs)

Summary tables for adverse events (AEs) included only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs. However, all safety data (including those from the pre- and post-treatment periods) were listed and those collected during the pre-treatment and post-treatment period were flagged. Any adverse events related to COVID were listed separately.

The following adverse event summaries were produced by treatment arm:

- Adverse events, regardless of study drug relationship by primary system organ class, preferred term and severity
- Adverse events with suspected study drug relationship by primary system organ class and by preferred term
- Serious adverse events regardless of study drug relationship, by primary system organ class and preferred term
- Serious adverse events with suspected study drug relationship, by primary system organ class and preferred term
- Adverse events leading to study drug discontinuation regardless of study drug relationship, by primary system organ class and preferred term

- Adverse events requiring dose adjustment or study-drug interruption regardless of study drug relationship, by primary system organ class and preferred term
- Adverse events requiring additional therapy regardless of study drug relationship, by primary system organ class and preferred term.
- An overall summary of type of AEs (e.g. serious, leading to study drug discontinuation, requiring dose adjustment or/and interruption) will be presented overall and by severe AEs and treatment arm.

All analyses were performed overall and by first formulation received/first switch/second switch (see Appendix 16.1.9-SAP-Section 2.2.4). COVID related adverse events by grouping and preferred term were also summarized.

9.9.2.3.2 Laboratory data

All laboratory values were converted into SI units. Clinical notable and extended ranges are defined for some laboratory values (refer Appendix 16.1.9-SAP-Table 2-3).

The following summaries were generated separately for hematology, biochemistry and urinary laboratory tests:

- shift tables using normal ranges to compare baseline to the worst on-treatment value.
- summary of patients with clinical notable and extended ranges.
- shift tables from baseline to two consecutive post-baseline values measured at least 7 days apart
- listing of all laboratory data with values flagged to show the corresponding normal/notable/extended ranges. Post-treatment assessments will be flagged.

For relevant parameters, observed values at end of each quarter (and changes from baseline) were summarized by descriptive statistics (n, mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum).

Creatinine clearance estimated using the Schwarz formula for patients < 18 years old and Cockcroft-Gault formula for patients ≥ 18 years old were displayed using relative change from baseline by categories.

Box plots of absolute value and change from baseline (absolute) were provided for the relevant parameters.

Liver Function Parameters

Liver function parameters of interest were total bilirubin (TBL), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and alkaline phosphatase (ALP). The number (%) of subjects with worst post-baseline values as per Novartis Liver Toxicity guidelines were summarized.

9.9.2.3.3 Vital signs

A listing of all vital sign assessments was produced. Notable values and those assessments collected outside of the on-treatment period were flagged.

The number of patients with notably abnormal vital signs were provided. The criteria for notably abnormal vital signs are defined in the Appendix 16.1.9-SAP-Section 5.4.

Descriptive statistics were tabulated per quarter using absolute change from baseline values for each vital sign measure, height, weight and BMI (see Appendix 16.1.9-SAP-Table 5-4 for time windows definition).

9.9.2.3.4 Other safety data

Data from ECG, ECHO, CMR, ocular and auditory examination were listed. Data from post-treatment period were flagged.

For ocular and auditory examinations shift tables were generated to present the worst post-baseline changes compared to baseline.

All data were listed.

9.9.3 Missing values

Missing data were not imputed.

9.9.4 Sensitivity analyses

No sensitivity analysis was performed.

9.9.5 Change to protocol specified analyses

Protocol section	Protocol description	Change in SAP	Rationale
7.7.5.2	Supportive analyses: However, in case of a high number of missing values, supplementary analyses using Complete Case Analysis approach were to be performed. A Complete Case Analysis excludes cases with missing laboratory values (for main hepatic and renal parameters) so that only complete cases were available. The estimates obtained from the complete case analysis were to be compared with the overall data set to view the effect of missing values on the estimates. If the number of	Complete case analysis was not performed	Since the sample size was too small, the number of patients to be included in this analysis was low.

	patients to be included in this analysis was low, the analysis was not to be conducted.		
7.7.6.2	(also tabulated for post treatment period)	Analysis not performed	Due to limited number of events, post treatment AE's are listed.
7.7.6.2	A table was to be also provided for incidence of treatment-emergent adverse events per total patient-years exposure. The number of AEs adjusted by time of exposure (events per year or events per month) was also to be tabulated.	Analysis not performed	Due to small sample size and non-interventional nature of the study, the AE's were observed to be under-reported
7.7.6.2	Additionally, AEs with suspected relationship to study drug, requiring dose adjustment, leading to drug interruption/discontinuation were to be specifically tabulated and listed, as well as AEs of special interest	All AEs of special interest were summarized.	In order to look at the overall safety profile.
7.7.6.3	Similar to AEs, the number of events related to lab abnormalities adjusted by time of exposure (events per year or events per month) were to be tabulated.	Analysis not performed	Due to small sample size and non-interventional nature of the study, the abnormalities are observed to be under-reported
7.7.6.4	Summary statistics of the number of transfusions, average amount RBC (in mL/kg/day) transfused per patient as well as average iron intake rate (in mg/kg/day) was to be provided.	Analysis not performed	Since the population is NTDT, the transfusion summary is not required.

Source: Appendix 16.1.9-SAP-Section 4

9.10 Quality control

Site monitoring

Formal site monitoring was performed as described in the Monitoring Plan for this study. The field monitor assured compliance monitoring.

Before study initiation, at a site initiation visit or at a physician's meeting, a Novartis representative or designee reviewed the protocol and eCRFs with the physicians and their staff. During the study, the field monitor visited the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol, the adherence to Good Clinical Practice, and the progress of enrollment. Key study personnel were available to assist the field monitor during these visits.

For details on data quality assurance, data collection, data recording and retention refer to Appendix 16.1.1-Protocol-Section 7.8.

10 Results

10.1 Participants

10.1.1 Disposition of patients

Overall, 45 patients were enrolled; 26 patients (57.8%) completed the treatment as per protocol and 19 patients (42.2%) discontinued the study. The majority of the patients discontinued the study treatment due to the physician's decision (7 patients [15.6%]), followed by 5 patients (11.1%) who were lost to follow-up, 4 patients (8.9%) due to the patient's or guardian's decision, and 3 patients (6.7%) due to administrative problems (Table 10-1).

A patient-specific disposition is summarized in the Listing 16.2.1-1.1.

Table 10-1 Patient disposition after start of deferasirox (Full Analysis Set)

Age Category: Overall	
Disposition	**All patients N=45 n (%)**
Completed treatment as per protocol	26 (57.8)
Premature study discontinuation	19 (42.2)
Administrative problems	3 (6.7)
Lost to follow-up	5 (11.1)
Physician's decision	7 (15.6)
Subject/guardian decision	4 (8.9)

Percentage is based on N
Source: Table 14.1-1.1.

10.1.2 Protocol deviations

A total of 10 patients reported at least 1 protocol deviation. All these deviations were related to COVID-19, including missed visits or assessments, visits conducted outside the site, or discontinuations due to COVID-19. Protocol deviations by patients are listed in Listing 16.2.2-1.1. The impact of COVID-19 indicates that the pandemic disrupted the study's protocol adherence, however this did not affect the study's overall data integrity and outcomes.

10.2 Demographic and disease history

10.2.1 Demography and baseline characteristics

Of the 45 patients enrolled, 21 (46.7%) were aged between 10 to ≤ 12 years and 24 (53.3%) patients were aged between > 12 to < 18 years at the time of enrollment. The median age of the patients was 13 years. A slightly higher number of males 24 (53.3%) were enrolled compared to females 21 (46.7%). The majority of the patients had Beta-thalassemia intermedia 28 (62.2%), followed by Alpha thalassemia intermedia (HbH disease) 10 (22.2%) (Table 10-2). The mean (SD) values for LIC and SF at baseline were 9.25(5.314) mg Fe/g dw liver, and 983.80 (679.45) µg/L, respectively. The individual demographic information is provided in Listing 16.2.4-1.1.

Table 10-2 Demographics and baseline data at start of deferasirox (Full Analysis Set)

Variable	All patients N=45
Age (Years)	
N	45
Mean	12.9
SD	2.40
Median	13.0
Minimum	10
Maximum	17
Age group (years) -n (%)	
10 - <= 12	21 (46.7)
>12 - < 18	24 (53.3)
Gender -n (%)	
Female	21 (46.7)
Male	24 (53.3)
Race -n (%)	
Caucasian	32 (71.1)
Asian	11 (24.4)
Other	2 (4.4)
Weight (kg)	
N	43
Mean	38.18
SD	13.761
Median	37.00
Minimum	15.5
Maximum	90.7
Height (cm)	
N	43
Mean	145.8
SD	15.90

Variable	All patients N=45
Median	148.0
Minimum	116
Maximum	181
BMI (kg/m2)	
N	43
Mean	17.39
SD	3.156
Median	17.40
Minimum	9.5
Maximum	27.7
Disease -n (%)	
Beta-thalassemia intermedia	28 (62.2)
HbE beta-thalassemia	4 (8.9)
Alpha thalassemia intermedia (HbH disease)	10 (22.2)
Other	3 (6.7)
Serum Ferritin (ug/L) -n (%)	
N	33
Mean	983.8
SD	679.45
Median	801.0
Minimum	201
Maximum	2713
Serum Ferritin (ug/L) -n (%)	
<500	11 (24.4)
>=500 - <1000	9 (20.0)
>=1000 - <2500	12 (26.7)
>=2500 - <5000	1 (2.2)
>=5000	0
Missing	12 (26.7)
LIC (mg Fe/g dw liver) -n (%)	
N	18
Mean	9.259
SD	5.3148
Median	8.300
Minimum	2.70
Maximum	23.20
LIC (mg Fe/g dw liver) -n (%)	
<=5	2 (4.4)
>5 – 7	6 (13.3)
>7 – 15	8 (17.8)

Variable	All patients N=45
>15	2 (4.4)
Missing	27 (60.0)

- Percentage is based on N
- Source: Table 14.1-3.1, Table 14.1-3.2

10.2.2 Medical history

Relevant medical history and current medical conditions by SOC and PT are represented in Table 14.1-4.1. Overall, the most common medical conditions by PT included Vitamine D deficiency (14 patients, 31.1%), splenomegaly (8 patients, 17.8%), splenectomy (8 patients, 17.8%), extramedullary hemopoiesis (5 patients, 11.1%), and hepatomegaly (5 patients, 11.1%).

10.2.3 Prior and concomitant therapies

Prior medications and concomitant medication by ATC and PT are reported in Table 14.3-2.1 and Table 14.3-2.2, respectively. Prior and concomitant medications are listed in Listing 16.2.5-2.1 and Listing 16.2.5-2.2, respectively.

Frequently used concomitant medications (≥15% of patients) included paracetamol 14 (31.1%) patients, folic acid 13 (28.9%) patients, hydroxycarbamide 10 (22.2%) patients, acetylsalicylic acid 8 (17.8%) patients and influenza vaccine 7 (15.6%) patients.

10.3 Extent of exposure

10.3.1 Duration of exposure excluding interruptions

The duration of exposure as of the LPLV (08-Jan-2025) is presented for the safety set in Table 10-3.

If a patient has received both formulations (at least one non-zero dose of each formulation), the patient’s records of dose information are counted in the corresponding formulation's column, and they contribute to the N of deferasirox DT or deferasirox FCT formulations. These patients also contribute to the total of both formulations under “All patients” column where all dosing information (irrespective of formulation) was considered.

Twenty-one patients were treated with deferasirox DT formulation only, 15 patients changed deferasirox formulation from DT to FCT, and 9 patients were treated with deferasirox FCT formulation only (Listing 16.2.5-1.1).

The median exposure to deferasirox (regardless of formulation) was 37.52 months (range: 3.2 to 68.7 months). Nineteen patients overall were treated for ≥ 48 months. Of the 36 patients treated with deferasirox DT, the median exposure to the deferasirox DT formulation was 18.28 months (range: 3.2 to 65.9 months), and of the 24 patients treated with FCT, the median exposure to the deferasirox FCT formulation was 29.52 months (range: 3.0 to 62.9 months) (Table 14.3-1.1).

The average dose of deferasirox by treatment formulation is presented in Table 14.3-1.2. The median of average actual dose of deferasirox DT was 19.79 mg/kg/day (range: 4.64-38.06 mg/kg/day) and the median of average actual dose of deferasirox FCT was 9.44 mg/kg/day (range: 1.22-24.08 mg/kg/day).

Dose administration records for individual patients are presented in Listing 16.2.5-1.1.

Table 10-3 Duration of exposure to study drug by treatment formulation (Safety Set)

	DFX DT (N=36)	DFX FCT (N=24)	All patients (N=45)
Duration of exposure in months - n (%)*			
<6	4 (11.1)	3 (12.5)	2 (4.4)
6 - <12	7 (19.4)	5 (20.8)	6 (13.3)
12 - <18	7 (19.4)	2 (8.3)	5 (11.1)
18 - <24	4 (11.1)	1 (4.2)	2 (4.4)
24 - <30	2 (5.6)	1 (4.2)	5 (11.1)
30 - <36	0	2 (8.3)	1 (2.2)
36 - <42	3 (8.3)	1 (4.2)	5 (11.1)
42 - <48	0	5 (20.8)	0
48 - <54	3 (8.3)	0	2 (4.4)
54 - <60	3 (8.3)	3 (12.5)	4 (8.9)
>=60	3 (8.3)	1 (4.2)	13 (28.9)
Patient exposure (months)			
n	36	24	45
Mean	26.32	29.54	37.79
SD	20.364	20.028	22.003
Median	18.28	29.52	37.52
Minimum	3.2	3.0	3.2
Maximum	65.9	62.9	68.7

A patient will only be counted if they have received at least one non-zero dose of the formulation.
In case where patients received both formulations, dose information is counted in the corresponding formulation under that column.
*Duration of exposure (month) = [(last date of exposure to the study drug formulation) – (date of first administration of the study drug formulation) + 1 day] / 30.4375
Source: Table 14.3-1.1.

10.3.2 Dose modifications or dose interruptions

The number of patients who had dose interruptions or dose changes with the corresponding reasons is summarized in Table 14.3-1.3.

Overall, 42 (93.3%) patients reported at least one dose change or interruption. Among the overall population, 36 (80.0%) patients reported at least one dose change, with the major reasons being protocol requirements in 34 (75.6%) patients and a decrease in Ferritin (or LIC) levels in 19 (42.2%) patients. Additionally, 29 (64.4%) patients of the overall population

reported at least one dose interruption. The primary reasons for dose interruptions, aside from the decrease in Ferritin (or LIC) levels in 19 (42.2%) patients, were AEs in 9 (20.0%) and scheduling conflicts in 6 (13.3%) patients.

10.4 Outcome data and main results

Safety results

For reporting adverse events, the on-treatment period for patients who receive the two formulations (deferasirox DT or deferasirox FCT), is divided into non-overlapping periods as 'First Formulation Received', 'First Switch', 'Second Switch', etc. based on the number of times a patient changes their formulation during the study. Therefore, adverse events reported at the time of treatment with each of the two deferasirox formulations are summarized. Fifteen patients initially treated with deferasirox DT switched to deferasirox FCT, and no patients switched from deferasirox FCT to deferasirox DT during the study.

Summary of overall AEs is presented in Table 10-4.

Table 10-4 Overall summary of adverse events (Safety Set)

Category	All patients N=45 n (%)
All deaths	0
On-treatment deaths	0
Adverse events	35 (77.8)
Suspected to be study drug-related	4 (8.9)
Serious adverse events	5 (11.1)
Suspected to be study drug-related	1 (2.2)
AEs leading to discontinuation	0
Suspected to be study drug-related	0
AEs requiring dose interruption and/or change	10 (22.2)
Suspected to be study drug-related	2 (4.4)
AEs requiring additional therapy	28 (62.2)
Suspected to be study drug-related	3 (6.7)
Hepatic and renal adverse events	1 (2.2)
Suspected to be study drug-related*	0
Hepatic adverse events	1 (2.2)
Suspected to be study drug-related	0
Renal adverse events	1 (2.2)
Suspected to be study drug-related	0

- Only AEs occurred in the corresponding timepoint (First formulation received, First Switch) and treatment formulation (DFX DT, DFX FCT) are included. For the overall group, all the AEs occurred during the study regardless of treatment formulation are recorded.

- Categories are not mutually exclusive. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
- On-treatment deaths: Deaths up to 30 days after the last study treatment are included.
-* : Adverse events related to hepatic (ALT, AST, total bilirubin, alkaline phosphatase) or renal (creatinine, creatinine clearance) functions that are suspected to be study drug related are considered
- Additional therapy includes all non-drug therapy and concomitant medications

Source: Table 14.3.1-1.2

Primary endpoint

10.4.1 AEs, SAEs, and AESIs

Overall, AEs regardless of relationship with study drug were reported in 35 (77.8%) patients, including 26 (72.2%) out of 36 patients who were treated with deferasirox DT and 7 (77.8%) out of 9 patients who were treated with FCT. Seven (46.7%) patients of 15 who had a First switch from DT to FCT reported AEs.

The most common AEs by SOC (> 20%) were infections and infestations 19 (42.2%) patients, respiratory, thoracic and mediastinal disorders 11 (24.4%) patients, general disorders and administration site conditions 10 (22.2%) patients and injury, poisoning and procedural complications 10 (22.2%) patients.

The 6 most common AEs by PT were upper respiratory tract infection in 9 (20.0%) patients, thrombocytosis, pyrexia, cough, rhinitis, and Vitamin D deficiency in 4 (8.9%) patients each (Table 14.3.1-2.1).

AEs suspected to be study drug related as assessed by the investigator were reported in 4 (8.9%) patients (Table 10-4, Listing 14.3.2-1.5). These AEs by PT included:

- A mild AE of abdominal pain upper in 2 (4.4%) patients was reported during the treatment with DFX DT. No action was taken for this AE in 1 patient while the other patient was administered with concomitant medication
- One (2.2%) patient each was reported with allergic dermatitis (moderate, treatment adjusted or temporarily interrupted, concomitant medication given); vomiting (severe, treatment temporarily interrupted, concomitant medication given); dizziness (moderate, treatment adjusted or temporarily interrupted); gastritis (mild, no action taken); and hyperchlorhydria (mild, concomitant medication given).

All the AEs suspected to be study drug related as assessed by the investigator were reported to be resolved.

No patients had AEs leading to study drug discontinuation (Listing 14.3.2-1.3).

The proportion of patients who experienced SAEs that were considered to be related to the study drug, was evaluated over a period of up to 5 years from the start of treatment. Overall, SAEs regardless of study drug relationship were reported in 5 (11.1%) patients and included SAEs by PT of gastroenteritis in 2 (4.4%) patients, portal vein thrombosis, post procedural haemorrhage, Influenza and vomiting, in 1 (2.2%) patient each (Table 14.3.1-2.3). Vomiting was the only

SAE suspected by investigator to be study drug related which occurred during the treatment with FCT formulation. Due to this SAE treatment was temporarily interrupted and concomitant medication was administered. All the SAEs were subsequently resolved (Table 14.3.1-2.4, Listing 16.2.7-1.1).

On-treatment deaths and serious adverse events by primary SOC, PT and treatment during the study are reported in Table14.3.1-13.

AEs occurring in individual patients are presented in Listing 16.2.7-1.1 Narratives for SAEs, and AESIs are provided in Section 14.3.3.

Table 10-5 Adverse Events and serious adverse events suspected to be study drug related (Safety set)

			First Formulation Received			
	Total (N=45)		DFX DT (N=36)		DFX FCT (N=9)	
Preferred term	All AEs	All SAEs	All AEs	All SAEs	All AEs	All SAEs
Total	4 (8.9)	1 (2.2)	3 (8.3)	0	1 (11.1)	1 (11.1)
Abdominal pain upper	2 (4.4)	0	2 (5.6)	0	0	0
Dermatitis allergic	1 (2.2)	0	1 (2.8)	0	0	0
Dizziness	1 (2.2)	0	1 (2.8)	0	0	0
Gastritis	1 (2.2)	0	1 (2.8)	0	0	0
Hyperchlorhydria	1 (2.2)	0	1 (2.8)	0	0	0
Vomiting	1 (2.2)	1 (2.2)	0	0	1 (11.1)	1 (11.1)

AE: Adverse event, SAE: Serious adverse event, DT: Dispersible tablet, FCT: Film-coated tablet.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
MedDRA Version 27.1 has been used for the reporting of adverse events.
Source: Table 14.3.1-2.2, Table 14.3.1-2.4, Listing 14.3.2-1.5

Overall, 9 (20.0%) patients reported AESIs, in which 1 (2.2%) patient each reported hearing loss, increased serum creatinine and increased liver transaminases, 7 (15.6%) patients reported AESIs of peripheral blood cytopenias (Table 14.3.1-2.9). None of the events were suspected to be related with the study treatment (Listing 14.3.2-1.6).

Deaths

No deaths occurred during the study (Table 14.3.1-1.2).

Secondary endpoints

10.4.2 Hepatic and renal safety

Overall, hepatic and renal AESIs regardless of study drug relationship were reported in 1 patient (2.2%), including increased ALT and increased blood creatinine (Table 14.3.1-1.2 and Table

14.3.1-2.8). Both events resolved with no action taken to deferasirox treatment. Narratives for this patient are included in Section 14.3.3.

An overall categorical analysis of hepatic laboratory values based on the worst post baseline values is presented in Table 10-6 and results of hepatic and renal lab parameters presented in below sections.

Table 10-6 Categorical analysis of hepatic laboratory values (Safety set)

	All subjects N=45 n (%)
Worst post-baseline values	
ALT >3x ULN	2 (4.4)
ALT >5x ULN	1 (2.2)
ALT >8x ULN	0
AST >3x ULN	1 (2.2)
AST >5x ULN	0
ALT or AST >3x ULN	2 (4.4)
ALT or AST >5x ULN	1 (2.2)
ALT or AST >8x ULN	0
Total bilirubin >2x ULN	33 (77.3)
Total bilirubin >3x ULN	19 (42.2)
Combined and concurrent values post-baseline	
ALT or AST >3x ULN &BILI >2x ULN	1 (2.2)
ALT or AST >3x ULN &BILI >2x ULN & ALP >=2x ULN	0
ALT or AST >3x ULN &BILI >2x ULN & ALP <2x ULN	1 (2.2)

- Concurrent measurements are those occurring in the same assessment sample.
- Worst post-baseline categories are overlapping, e.g. "ALT >3X ULN" includes all subjects from category "ALT >5xULN

Source: Table 14.3-4.8

10.4.2.1 Alanine aminotransferase (ALT)

No patients in the study had an episode of ALT >5×ULN in at least 2 consecutive post-baseline measurements at least 7 days apart (Table 14.3-4.6). Changes from baseline to highest post-baseline values in ALT of patients on study treatment are presented in Table 10-7.

The baseline data was available for 37/45 (82.2%) patients. The highest post-baseline ALT values showed that 23 patients (51.1%) had values ≤ULN, 13 patients (28.9%) had values >ULN-≤2×ULN, 6 patients (13.3%) had values >2×ULN-≤4×ULN, 2 patients (4.4%) had values >4×ULN-≤6×ULN. 1 patient (2.2%) had values in the notable range (>5×ULN and >2× baseline value).

Table 10-7 Shifts in ALT (U/L) from baseline to highest post-baseline values (Safety set)

Deferasirox (N=45)	Baseline n (%)	<=ULN (1) n (%)	>ULN-<=2×ULN (1) n (%)	>2×ULN-<=4×ULN (1) n (%)	>4×ULN-<=6×ULN (1) n (%)	>6×ULN (1) n (%)	Notable range (2) n (%)	Extended range (2) n(%)	Missing (1) n(%)
≤ULN	29 (64.4)	19 (65.5)	5 (17.2)	3 (10.3)	1 (3.4)	0	0	0	1 (3.4)
>ULN - ≤2×ULN	4 (8.9)	1 (25.0)	2 (50.0)	1 (25.0)	0	0	0	0	0
>2×ULN - ≤4×ULN	3 (6.7)	0	2 (66.7)	0	1 (33.3)	0	1 (33.3)	0	0
>4×ULN - ≤6×ULN	0	0	0	0	0	0	0	0	0
>6×ULN - ≤8×ULN	1 (2.2)	0	0	1 (100.0)	0	0	0	0	0
>8×ULN - ≤10×ULN	0	0	0	0	0	0	0	0	0
>10×ULN	0	0	0	0	0	0	0	0	0
Missing	8 (17.8)	3 (37.5)	4 (50.0)	1 (12.5)	0	0	0	0	0
Total	45 (100.0)	23 (51.1)	13 (28.9)	6 (13.3)	2 (4.4)	0	1 (2.2)	0	1 (2.2)

ALT: Alanine aminotransferase, ULN: Upper Limit of Normal

Baseline is defined as the last non-missing value prior or on the day of first dose.

Baseline percentage is based on N. Percentage for highest post-Baseline value is based on Baseline n.

Notable range: > 5xULN and > 2xbaseline value. - Extended range: > 10×ULN and > 2×baseline value.

(1) Within each classification, patients are only counted in the highest category, as listed from left (lowest) to right (highest: >10 ULN), i.e. categories are mutually exclusive.

(2) Includes all patients who fulfilled condition.

Source: Table 14.3-4.5

10.4.2.2 Aspartate aminotransferase (AST)

Changes from baseline to highest post-baseline values in AST of patients on study treatment are presented in Table 10-8.

The baseline data was available for 35/45 (77.8%) patients.

The highest post-baseline AST values showed that 14 patients (31.1%) had values ≤ULN, 25 patients (55.6%) had values >ULN-≤2×ULN, 5 patients (11.1%) had values >2×ULN-≤4×ULN. No patient fulfilled the condition of notable (defined as >5×ULN and >2×baseline value) or extended range (defined as >10×ULN and 2×baseline value) in AST (Table 14.3-4.7).

Table 10-8 Shifts in AST (U/L) from baseline to highest post-baseline values (Safety set)

		Highest post-baseline value				
Deferasirox (N=45)	**Baseline n (%)**	**<=ULN (1) n (%)**	**>ULN - <=2xULN (1) n (%)**	**>2xULN - <=4xULN (1) n (%)**	**>4xULN (1) n (%)**	**Missing (1) n (%)**
<=ULN	24 (53.3)	11 (45.8)	11 (45.8)	1 (4.2)	0	1 (4.2)
>ULN - <=2xULN	7 (15.6)	0	6 (85.7)	1 (14.3)	0	0
>2xULN - <=4xULN	4 (8.9)	0	3 (75.0)	1 (25.0)	0	0
>4xULN - <=6xULN	0	0	0	0	0	0
>6xULN - <=8xULN	0	0	0	0	0	0
>8xULN - <=10xULN	0	0	0	0	0	0
>10xULN	0	0	0	0	0	0
Missing	10 (22.2)	3 (30.0)	5 (50.0)	2 (20.0)	0	0
Total	45 (100.0)	14 (31.1)	25 (55.6)	5 (11.1)	0	1 (2.2)

AST: Aspartate aminotransferase, ULN: Upper Limit of Normal

Baseline is defined as the last non-missing value prior or on the day of first dose.

Baseline percentage is based on N. Percentage for highest post-Baseline value is based on Baseline n.

Notable range: > 5×ULN and > 2×baseline value. - Extended range: > 10×ULN and > 2×baseline value.

(1) Within each classification, patients are only counted in the highest category, as listed from left (lowest) to right (highest: >10 ULN), i.e. categories are mutually exclusive.

(2) Includes all patients who fulfilled condition.

Source: Table 14.3-4.7

10.4.2.3 Total bilirubin

Changes from baseline to two consecutive highest post-baseline values at least 7 days apart in total bilirubin of patients on study are presented in Table 10-9.

The baseline data was available for 31/45 (68.9%) patients. Majority of patients had elevated total bilirubin at baseline. The highest two consecutive post-baseline total bilirubin values showed that 2 patients (4.4%) had values ≤ULN, 9 patients (20.0%) had values >ULN-≤2×ULN, 18 patients (40.0%) had values >2×ULN-≤4×ULN, 6 patients (13.3%) had values >4×ULN-≤6×ULN (Listing 16.2.7-1.1).

Table 10-9 Shifts in total bilirubin (µmol/L) from baseline to two consecutive post-baseline values at least 7 days apart (Safety set)

	Two consecutive post-baseline values measured at least 7 days apart						
Deferasirox (N=45)	**Baseline n (%)**	**Two consec. <=ULN n (%)**	**Two consec. >ULN-<=2×ULN n (%)**	**Two consec. >2×ULN-<=4×ULN n (%)**	**Two consec. >4×ULN-<=6×ULN n (%)**	**Two consec. >6×ULN n (%)**	**Missing n(%)**
<=ULN	5 (11.1)	0	2 (40.0)	0	1 (20.0)	0	2 (40.0)
>ULN-<=2×ULN	12 (26.7)	1 (8.3)	7 (58.3)	3 (25.0)	0	0	1(8.3)
>2×ULN-<=4×ULN	12 (26.7)	0	0	7 (58.3)	3 (25.0)	0	2 (16.7)
>4×ULN-<=6×ULN	2 (4.4)	0	0	0	2 (100.0)	0	0
>6×ULN-<=8×ULN	0	0	0	0	0	0	0
>8×ULN-<=10×ULN	0	0	0	0	0	0	0
>10×ULN	0	0	0	0	0	0	0
Missing	14 (31.1)	1 (7.1)	0	8 (57.1)	0	0	5 (35.7)
Total	45 (100.0)	2 (4.4)	9 (20.0)	18 (40.0)	6 (13.3)	0	10 (22.2)

ULN: Upper Limit of Normal

Baseline is defined as the last non-missing value prior or on the day of first dose.

Baseline percentage is based on N. Percentage for 2 consecutive values column is based on Baseline n.

Within each classification, patients are only counted in the highest category, as listed from left (lowest) to right (highest: Two consec. >10 ULN), i.e. categories are mutually exclusive

Missing category is defined as patients are not meeting any of the above criteria or no post-baseline record.

Source: Table 14.3-5.9

10.4.2.4 Hy's Law case

Patient [redacted] ([redacted] year old male with beta-thalassemia intermedia) met the definition of biochemical Hy's Law criteria on Day 197, with a combined and concurrent worst post-baseline value of ALT or AST >3×ULN (ALT was > 5xULN) and total bilirubin >2×ULN,

without evidence of cholestasis (ALP <2×ULN) (Table 14.3-4.8, Figure 14.3-1.9, Listing 16.2.8-3.1). This case was presented in the 3rd annual safety report. Based on the World Health Organization–Uppsala Monitoring Centre (WHO-UMC) causality assessment criteria, Novartis assessed this case as 'unlikely' drug induced liver injury (DILI) related to study medication for the following reasons: 1) the patient had medical history of mild hepatic siderosis (diagnosed on [redacted]) manifested by hepatosplenomegaly, and intermittent elevated liver function tests; 2) patient had active Epstein-Barr virus infection; 3) patient had abnormal liver function assessments at baseline with ALT> 1×ULN, AST> 1×ULN and total bilirubin >2×ULN; 4) Moderate severity cholelithiasis was reported by the investigator on Day 196, 1 day before the biochemical Hy's Law criteria were met. On Day 252, ALT value returned to normal; AST and ALP were within normal range as well. Total bilirubin remained elevated throughout the study duration. Cholelithiasis reported resolved on Day 890. The patient completed the study on Day 1887 (Listing 16.2.7-1.1).

10.4.2.5 Gall stones

Four patients had an AE of cholelithiasis reported during the study. None of the AEs of cholelithiasis were suspected to be study drug related. In 3 patients the AE of cholelithiasis was reported during treatment with deferasirox DT and were mild or moderate in severity and in one patient event occurred more than a year after study treatment was stopped and was severe. The 2 mild cases of cholelithiasis were given non-drug therapy, the moderate case was treated with concomitant medication and the severe case was treated with concomitant medication and the non-drug therapy (Listing 16.2.7-1.1).

10.4.2.6 Serum creatinine and creatinine clearance

No concerning decreases in renal function have been observed based on SCr and CrCl monitoring (Table 10-10, Table 10-11).

The baseline data for serum creatinine was available for 37/45 (82.2%) patients.

Of the 36 (80.0%) patients with normal SCr at baseline, 34 (94.4%) patients remained with normal SCr values, 1 (2.8%) patient had an increase to >ULN to ≤ 2×ULN and 1 (2.8%) patient had missing post baseline value. The only patient with SCr >ULN to ≤ 2×ULN at baseline reverted to normal. Of the 8 (17.8%) patients with missing assessment of serum creatinine at baseline, all had normal SCr post-baseline (Table 10-10).

No patient had notable range (defined as two consecutive values >ULN and >33% increase from baseline) in SCr. (Table 14.3-4.4).

The baseline data for CrCl was available for 27/45 (60.0%) patients. The lowest post-baseline CrCl values showed that 1 patient (2.2%) had two consecutive values of ≥ 60 to <90 mL/min, 1 patient (2.2%) had one value of ≥ 60 to <90 mL/min, remaining patients had CrCL ≥ 90 mL/min (Table 10-11).

No patient fulfilled the conditions for CrCl decrease to notable (two consecutive values of <60 mL/min measured at least 7 days apart) or extended (two consecutive values of <40 mL/min measured at least 7 days apart) range (Table 14.3-5.4).

Listings of laboratory values by patient for serum creatinine and creatinine clearance are presented in Listing 16.2.8-3.1 and Listing 16.2.8-4.1, respectively.

Table 10-10 Shifts in serum creatinine (µmol/L) from baseline to highest post-baseline values (Safety set)

		Highest post-baseline value				
Deferasirox (N=45)	**Baseline n (%)**	**<=ULN (1) n (%)**	**>ULN-<=2xULN (1) n (%)**	**>2xULN (1) n (%)**	**Notable range (2) n (%)**	**Missing (1) n (%)**
<=ULN	36 (80.0)	34 (94.4)	1 (2.8)	0	0	1 (2.8)
>ULN-<=2xULN	1 (2.2)	1 (100.0)	0	0	0	0
>2xULN-<=4xULN	0	0	0	0	0	0
>4xULN-<=6xULN	0	0	0	0	0	0
>6xULN-<=8xULN	0	0	0	0	0	0
>8xULN-<=10xULN	0	0	0	0	0	0
>10xULN	0	0	0	0	0	0
Missing	8 (17.8)	8 (100.0)	0	0	0	0
Total	45 (100.0)	43 (95.6)	1 (2.2)	0	0	1 (2.2)

ULN: Upper Limit of Normal

Baseline is defined as the last non-missing value prior or on the day of first dose.

Baseline percentage is based on N. Percentage for highest post-baseline value is based on Baseline n

Notable range: >33% increase from baseline and >ULN at two consecutive measurements at least 7 days apart.

(1) Within each classification, patients are only counted in the highest category, as listed from left (lowest) to right (highest: >10 ULN), i.e. categories are mutually exclusive.

(2) Includes all patients who fulfilled condition.

Source: Table 14.3-4.3

Table 10-11 Shifts in creatinine clearance (mL/min) from baseline to lowest post-baseline values (Safety set)

		Lowest post-baseline value (mL/min)								
Deferasirox (N=45)	**Baseline n (%)**	**One value <60 (1) n (%)**	**Two consec. >=60-<90 (1) n (%)**	**One value >=60 - <90 (1) n (%)**	**Two consec. >=90-<160 (1) n (%)**	**One value >=90 - <160 (1) n (%)**	**One value >=160 (1) n (%)**	**Notable range (2) n (%)**	**Extended range (2) n (%)**	**Missing (1) n (%)**
< 60	0	0	0	0	0	0	0	0	0	0
60 - < 90	0	0	0	0	0	0	0	0	0	0
90 - < 160	6 (13.3)	0	0	0	4 (66.7)	2 (33.3)	0	0	0	0
>=160	21 (46.7)	0	0	0	7 (33.3)	3 (14.3)	10 (47.6)	0	0	1 (4.8)
Missing	18 (40.0)	0	1(5.6)	1 (5.6)	5 (27.8)	5 (27.8)	6 (33.3)	0	0	0
Total	45 (100.0)	0	1(2.2)	1 (2.2)	16 (35.6)	10 (22.2)	16 (35.6)	0	0	1 (2.2)

Baseline percentage is based on N. Percentage for lowest post-baseline value is based on Baseline n

Baseline value is defined to be the last available value prior to or on the day of first dose of study drug

Notable range: Two consecutive values measured at least 7 days apart <60 mL/min

Extended range: Two consecutive values measured at least 7 days apart <40 mL/min

For two consecutive values, measurements must be at least 7 days apart.

(1) Within each classification, patients are only counted in the lowest category, as listed from left (lowest) to right (highest: >=160mL/min), i.e. categories are mutually exclusive.

(2) Includes all patients who fulfilled condition.Source: Table 14.3-5.4

10.4.3 Growth and development

Growth and development was assessed over the period of approximately 5 years for each patient (unless the patient discontinued the study early).

10.4.3.1 Height, weight, and BMI

Raw values, absolute and relative changes from baseline to last post-baseline values were analyzed by quarter intervals. As expected, the data indicates an increase in weight, height, and BMI from baseline to Quarter 20 (Year 5).

For female patients: The mean height increased from 142.9 cm to 156.7 cm, representing an absolute change of 21.3 and a relative change of 15.87. The mean weight increased from 37.22 kg to 50.33 kg, representing an absolute change of 20.67 and a relative change of 72.37. The

mean BMI increased from 17.77 kg/m² to 20.50 kg/m², representing an absolute change of 4.33 and a relative change of 27.56 (Table 14.3-7.3).

For male patients: The mean height increased from 148.4 cm to 164.9 cm, representing an absolute change of 16.6 and a relative change of 11.90. The mean weight increased from 39.02 kg to 48.10 kg, representing an absolute change of 12.51 and a relative change of 39.57. The mean BMI increased from 17.07 kg/m² to 17.33 kg/m², representing an absolute change of 1.57 and a relative change of 11.14 (Table 14.3-7.2)

Height velocity for females and males is presented in Table 14.3-8.10 and Table 14.3-8.9, respectively.

Table 10-12 Summary of mean height, weight and BMI for males and females by quarter

Analysis quarter (year)	n	Mean height (cm)	Mean weight (kg)	Mean BMI
Females (N=21)				
Baseline	20	142.9	37.22	17.77
Quarter 4 (year 1)**(1)**	11	140.7	35.08	17.11
Quarter 8 (year 2)	13	146.5	39.05	17.82
Quarter 12 (year 3)	10	154.2	45.50	18.95
Quarter 16 (year 4)	4	151.5	44.70	19.35
Quarter 20 (year 5)	3	156.7	50.33	20.50
Males (N=24)				
Baseline	23	148.4	39.02	17.07
Quarter 4 (year 1)	16	152.4	40.91	17.16
Quarter 8 (year 2)	14	152.8	39.30	16.54
Quarter 12 (year 3)	15	159.4	48.58	18.52
Quarter 16 (year 4)	11	163.7	51.50	18.95
Quarter 20 (year 5)	7	164.9	48.10	17.33

- Baseline is defined as the last non-missing value prior or on the day of first dose.
- n is number of patients who had Baseline and post Baseline at a given time point.
- **(1):** For quarter 4, n=11 patients for weight (kg) and n=10 patients for height (cm) and BMI
- Source: Table 14.3-7.2, Table 14.3-7.3

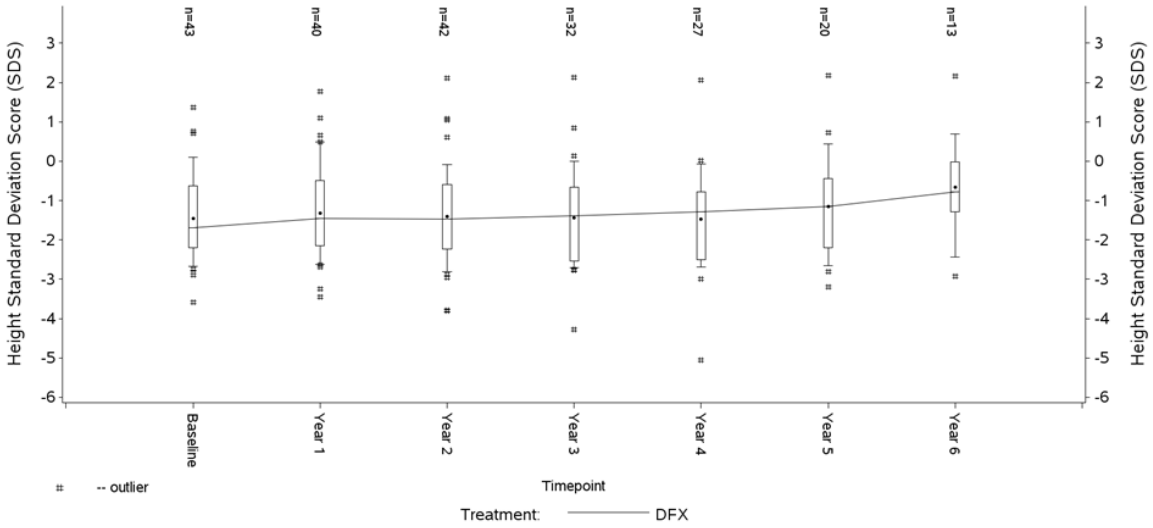
The summary of growth data by time window from baseline to Year 5 for the age categories 10 - <= 12 and >12 - < 18, is presented below (Table 14.3-8.11). Notably Low or High categories are defined as values below the 5th percentile (SDS < -1.645) and above the 95th percentile (SDS > 1.645), respectively, of the CDC US Growth Charts:

- **For patients aged 10 - <= 12**: mean height SDS changed from -1.5624 to -1.2244, with 57.1% categorized as notably low at baseline and 33.3% at Year 5. The mean weight SDS changed from -1.7882 to -1.5195, with 57.1% categorized as notably low at baseline and 42.9% at Year 5. The mean BMI SDS changed from -1.2067 to -1.0522, with 19.0% categorized as notably low at baseline and 23.8% at Year 5

- **For patients aged >12 - < 18**: From baseline to Year 5, the mean height SDS increased from -1.3739 to -0.9634, with 41.7% categorized as notably low at baseline and 4.2% at Year 5. The mean weight SDS changed from -1.4142 to -1.4014, with 45.8% categorized as notably low at baseline and 8.3% at Year 5. The mean BMI SDS decreased from -0.9462 to -1.3000, with 20.8% categorized as notably low at baseline and 8.3% at Year 5.

Shift tables for height SDS and BMI SDS are provided in Tables 14.3-8.12 and Table 14.3-8.13, respectively. Majority of patients remained in the same SDS category as at baseline (low or normal). Figures 10-1, Figures 10-2, and Figures 10-3 display the box plots of growth data (height SDS, height velocity SDS, BMI SDS) in yearly intervals from baseline to last on study assessment timepoint. Overall, it indicates stable height SDS, height velocity SDS and BMI SDS during the study period, with no change in proportion of patients with SDS values < 5th percentile (< -1.645).

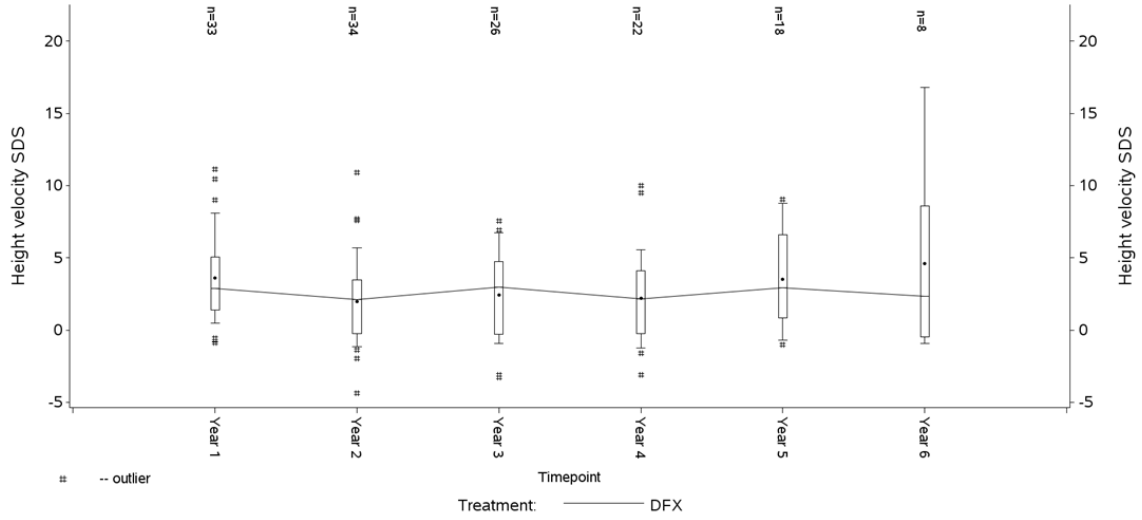
Figure 10-1 Box plot of height SDS by time point during the study (Safety Set)



- The length of the box represents the interquartile range (the distance between the 25th and the 75th percentiles), the whiskers extend to the 10th and 90th percentiles, means are presented as dots and medians are connected over time points.
- Baseline is defined as the last non-missing value prior or on the day of first dose of study treatment.

Source: Figure 14.3-1.11

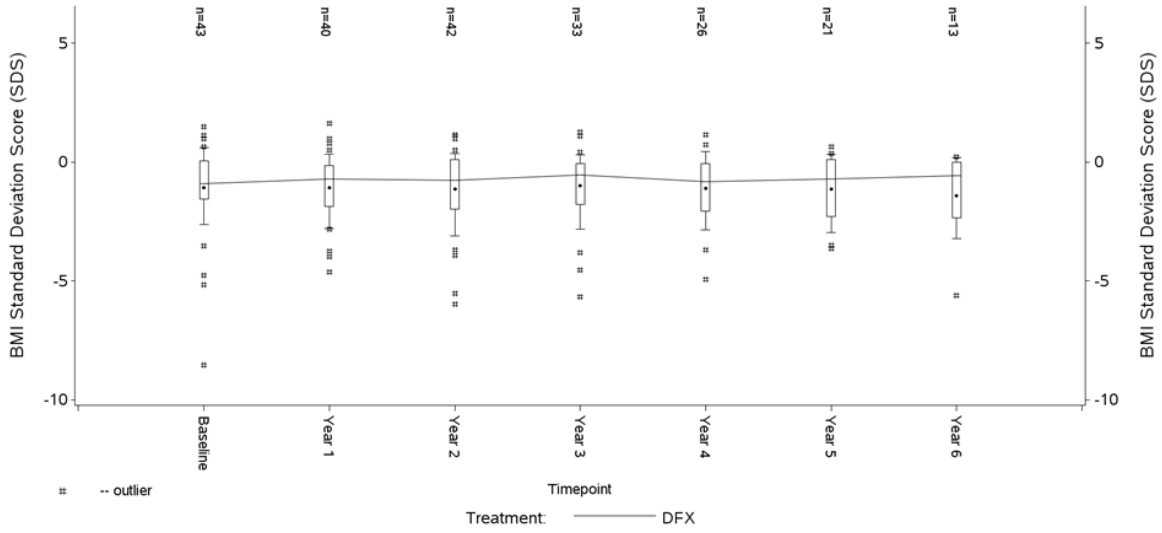
Figure 10-2 Box plot of height velocity SDS by time point during the study



- The length of the box represents the interquartile range (the distance between the 25th and the 75th percentiles), the whiskers extend to the 10th and 90th percentiles, means are presented as dots and medians are connected over time points.
- Baseline is defined as the last non-missing value prior or on the day of first dose of study treatment.

Source: Figure 14.3-1.11

Figure 10-3 Box plot of BMI SDS by time point during the study



- The length of the box represents the interquartile range (the distance between the 25th and the 75th percentiles), the whiskers extend to the 10th and 90th percentiles, means are presented as dots and medians are connected over time points.
- Baseline is defined as the last non-missing value prior or on the day of first dose of study treatment.

Source: Figure 14.3-1.11.

The individual growth curves showed continuous growth in male and female pediatric patients from both age cohorts (10-<=12 and >12-<18) during deferasirox treatment, although growth trends tended to lie within the lower percentiles of US Clinical Growth Charts (Figure 14.3-1.10).

Growth analysis on study CICL670A0107E

- As required per protocol in order to compare the pediatric growth from the current study with historical data in patients with transfusional iron overload, growth analysis was also conducted in pediatric patients aged 10-<18 years from the historical study CICL670A0107E: A 4-year open label, non-comparative extension to a randomized, comparative, open label phase III trial on efficacy and safety of long-term treatment with ICL670 (5 to 40 mg/kg/day) in comparison with deferoxamine (20 to 60 mg/kg/day) in β-thalassemia patients with transfusional hemosiderosis.
- Similar patterns of change over time was observed in CICL670A0107E study when summary of growth data was generated by time window (Table 14.3-8.11a).
- Shift tables for height SDS and BMI SDS are provided in Tables 14.3-8.12a and Table 14.3-8.13a, respectively. Majority of patients remained in the same SDS category as at baseline (low or normal) which is similar to what is observed in this study.
- Figure 14.3-1.11a displays the box plots of growth data (height SDS, height velocity SDS, BMI SDS) in yearly intervals from Baseline to last on study assessment timepoint for CICL670A0107E study. Stable height SDS, height velocity SDS and BMI SDS was observed during the study period, with no change in proportion of patients with SDS values < 5th percentile (< -1.645) similarly to the present study results.
- The growth curves for Study CICL670A0107E showed continuous growth in male and female pediatric patients from both age cohorts (10-12 and >12-<18) during deferasirox treatment, although growth trends tended to lie within the lower percentiles of US Clinical Growth Charts (Figure 14.3-1.10a). A similar growth pattern in male and female pediatric patients had been reported in the present study.

10.4.3.2 Tanner stages

Limited patient data was available for Tanner stage analyses, with most patients having only 1 to 3 values. The data on Tanner stages based on pubic hair and breasts for females are presented per age and Tanner category in Table 14.3-9.6 and Table 14.3-9.8, respectively. The data on Tanner stages based on pubic hair and genitals for males are presented per age and Tanner category in Table 14.3-9.5 and Table 14.3-9.7, respectively.

Shift tables from baseline to last on-study value for pubic hair and breasts of female patients are presented in Table 14.3-9.2 and Table 14.3-9.4, respectively. Shift tables from baseline to last on-study value for pubic hair and genitals of male patients are presented in Table 14.3-9.1 and Table 14.3-9.3, respectively.

Eleven patients (5 females and 6 males) had Tanner stage assessments at baseline and at least 1 post-baseline assessment (Listing 16.2.9-1.3 and Listing 16.2.9-1.2).

Of the 5 female patients who had baseline and post-baseline assessments:

Female Patients:

- One patient ([redacted]; age [redacted]) had Tanner 2 for breasts at baseline and did not change at post-baseline assessment. Pubic hair was at Tanner 2 pre-baseline but was not assessed thereafter.
- One patient ([redacted]; age [redacted]) had Tanner 1 for breasts and pubic hair at baseline, developed to Tanner 2 at the first post-baseline assessment and Tanner 3 at a later post-baseline assessment.
- One patient ([redacted]; age [redacted]) had Tanner 2 for breasts and pubic hair at baseline, which developed up to Tanner 5 by the fifth post-baseline assessment.
- One patient ([redacted]; age [redacted]) had Tanner 5 for breasts and pubic hair at baseline.
- One patient ([redacted]; age [redacted]) had Tanner 1 for breasts at Day 1, which developed to Tanner 2 at the first and second post-baseline assessments, remaining at that level at the third post-baseline assessment. Pubic hair was at Tanner 1 at baseline, remained at Tanner 1 at the first and second post-baseline assessments, and developed to Tanner 3 at the third post-baseline assessment.

Male Patients:

- One patient ([redacted]; age [redacted]) had Tanner 3 for genitals and Tanner 4 for pubic hair at baseline, which developed to Tanner 4 for genitals and Tanner 5 for pubic hair at post-baseline assessment.
- One patient ([redacted]; age [redacted]) had Tanner 2 for genitals and Tanner 1 for pubic hair at baseline, which developed to Tanner 3 for genitals and Tanner 2 for pubic hair at post-baseline assessment. Pubic hair developed to Tanner 3 at the third post-baseline assessment.
- One patient ([redacted]; age [redacted]) had Tanner 3 for genitals and Tanner 2 for pubic hair at baseline, which developed to Tanner 4 for genitals and Tanner 5 for pubic hair at subsequent assessments, with genitals developing to Tanner 5 one year later.
- One patient ([redacted]; age [redacted]) had Tanner 1 for genitals and pubic hair at baseline, which developed to Tanner 2 for genitals at post-baseline assessment, remaining at that level in the subsequent assessment. Pubic hair developed from Tanner 1 to Tanner 5.
- One patient ([redacted]; age [redacted]) had Tanner 1 for genitals and pubic hair at baseline and remained at this level during the post-baseline assessment.
- One patient ([redacted]; age [redacted]) had Tanner 1 for genitals and pubic hair at baseline and reported Tanner 4 for both at post-baseline assessment.

Of the patients without available baseline Tanner assessment, patient [redacted] ([redacted] years, [redacted] male patient), with HbE beta-thalassemia, had reported medical condition of delayed puberty (body height below normal and delayed puberty) diagnosed on [redacted] before enrollment in the study on [redacted] The patient started deferasirox treatment on 03

Nov 2014. At baseline ([redacted]), this patient weighed [redacted] kg and had a height of [redacted]. Tanner stage at baseline was not reported. On Day 198 ([redacted]) he had mild growth hormone deficiency, not suspected to be related to the study drug by the investigator that continued at the same grade throughout the study course without treatment. This patient had only post baseline assessments and had Tanner 1 based on pubic hair post-baseline ([redacted]) and remained at this level until the last assessment ([redacted]) (Listing 14.3-2.1). Additionally, this patient had not reached Tanner stage 2 for genitals by age [redacted]; however, this was reached at age [redacted] (Listing 14.3-2.3).

Number and percentages of patients who were below, within and above the Marshal standards (mean age in years ± 2 SD) for each Tanner stages by gender were:

For female patients:

- At baseline, none were below and within, and 4 patients (19.0%) were above the Marshall standards, while at Year 5, 1 patient (4.8%) was within, and none were below and above the Marshall standards for pubic hair Tanner Stages (Table 14.3-9.10).
- At baseline, none were below, 4 patients (19.0%) were within, and 4 patients (19.0%) were above the Marshall standards for breasts, while at Year 5, 1 patient (4.8%) was within, none were below and above the Marshall standards for breasts Tanner Stages (Table 14.3-9.12).

For male patients:

- At baseline, 1 patient (4.2%) was below, 5 patients (20.8%) were within, and 4 patients (16.7%) were above the Marshall standards, while at Year 5, none were below, 2 patients (8.3%) were within, and 3 patients (12.5%) were above the Marshall standards for pubic hair Tanner Stages (Table 14.3-9.9).
- At baseline, none were below, 3 patients (12.5%) were within, and 7 patients (29.2%) were above the Marshall standards for genitals, while at Year 5, none were below and within and 1 patient (4.2%) was above the Marshall standard for genitals Tanner Stages (Table 14.3-9.11).

10.4.4 Other safety parameters

Although some patients had abnormal laboratory values noted (high or low), none were considered clinically meaningful. Other clinical laboratory data are presented in Listing 16.2.8-3.1. ECG listed in Listing 16.2.9-6.1 with no significant abnormalities reported. Echocardiography data is listed in Listing 16.2.9-7.1 with 1 clinically significant abnormality. Urine protein results listed in Listing 16.2.8-5.1 with no significant abnormalities.

Hematology

Primary hematology variables are presented in Listing 16.2.8-2.1. Differential counts for hematologic parameters are presented in Listing 16.2.8-2.2.

At baseline, 4 patients (8.9%) had low absolute neutrophils, 29 patients (64.4%) had normal, 8 patients (17.8%) had high, and 4 patients (8.9%) had missing values. Of the 29 patients (64.4%) who had normal absolute neutrophils at baseline, 5 patients (17.2%) shifted to low

post-baseline values, 6 (20.7%) patients shifted to high post-baseline values and 1 (3.4%) patient had both low and high values.

At baseline, 2 patients (4.4%) had low platelets, 29 patients (64.4%) had normal, 9 patients (20.0%) had high, and 5 patients (11.1%) had missing platelet counts. Of the 29 patients (64.4%) who had normal platelets at baseline, 1 patient (3.4%) shifted to low post-baseline values, 7 (24.1%) patients shifted to high post-baseline values and 1 (3.4%) patient had both low and high values (Table-14.3-3.3 and Listing 16.2.8-2.2).

Audiometric assessment

Audiometric assessment was documented in 24 patients (Listing 16.2.9-2.5).

For the audiometric examination, of the 45 patients, 8 (17.8%) had normal results, 1(2.2%) had insignificant findings and 36 (80.0%) were missing at baseline. For post-baseline, 18 (40.0%) had normal results, 1 (2.2%) had significant findings, and 26 (57.8%) had missing data reported at worst post-baseline assessment (Table 14.3-10.4).

One patient ([redacted]) had a clinically significant auditory abnormality. Diagnosed with beta thalassemia intermedia and not receiving chelation before the study, the patient had no relevant medical history or concomitant medications. Baseline audiometric testing was missing. On Day 85 ([redacted]), mild hypoacusis was reported, not suspected to be related to deferasirox DT treatment (Listing 16.2.7-1.1). The patient continued treatment without any intervention for the event and discontinued deferasirox DT on Day 233 ([redacted]) due to unavailable MRI T2* results to confirm iron overload. For further information refer to case narratives in Section 14.3.3.

Ophthalmological examinations

Ocular assessments were documented for 20 patients (Listing 16.2.9-2.4).

For the ocular examination, of the 45 patients, 6 (13.3%) had normal results, 1 (2.2%) had insignificant findings, 1 (2.2%) had significant findings and 37 (82.2%) were missing at baseline. For post-baseline 13 (28.9%) had normal results, 3 (6.7%) had insignificant findings, and 29 (64.4%) had missing data reported at worst post-baseline assessment (Table 14.3-10.4).

One patient ([redacted]) had a clinically significant ocular abnormality (myopia) prior to receiving treatment on Study Day -5 ([redacted]) which was ongoing at the time of enrollment. This patient had no post-baseline assessment and was not reported with any ocular adverse event.

10.4.5 Long term efficacy

The long-term efficacy of deferasirox was measured by SF and LIC among 45 patients. The results showed that 19 patients (42.2%) achieved SF levels below 300 µg/L, and 15 patients (33.3%) achieved LIC levels below 3 mg Fe/g dw liver. Additionally, 4 patients (8.9%) restarted deferasirox treatment after temporary interruption due to SF levels below 300 µg/L or LIC levels below 3 mg Fe/g dw liver (Table 10-13).

Box plot of absolute change from baseline for SF and LIC values by timepoint are represented in Figure 10-4 and Figure 10-5, respectively.

Among the patients with at least one post-baseline, 19 (43.2%) out of 44 patients achieved SF levels below 300 ug/L, and 15 (51.7%) out of 29 patientss achieved LIC<3 mg Fe/g dw liver. 4 patients (9.1%) out of 44 patients had to restart deferasirox treatment after temporary interruption due to SF<300 ug/L or LIC<3 mg Fe/g dw liver.

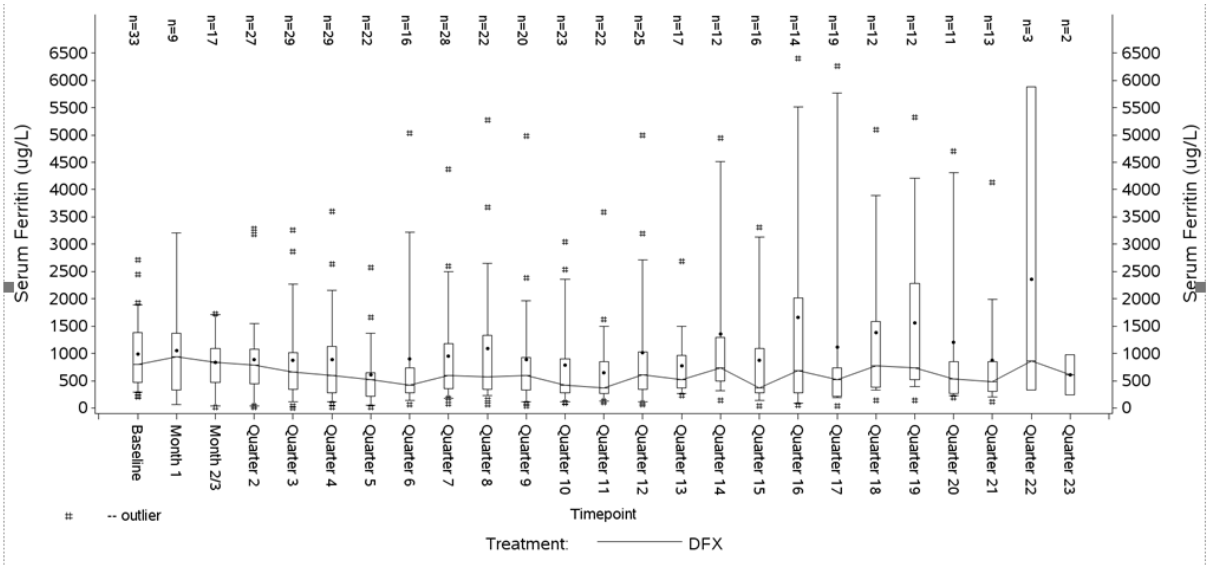
Table 10-13 Number and frequency of SF<300 ug/L, LIC<3 mg Fe/g dw liver and restarting deferasirox treatment after temporary interruption due to SF<300 ug/L or LIC<3 mg Fe/g dw liver (FAS)

Long term efficacy of DFX measured by serum ferritin and LIC	All patients N=45 n (%)
SF <300 ug/L	19 (42.2)
LIC <3 mg Fe/g dw liver	15 (33.3)
Restarting deferasirox treatment after temporary interruption due to SF <300 ug/L or LIC <3 mg Fe/g dw liver	4 (8.9)

- Counts and frequencies will be provided for each criteria happening at any time during the study.
- Subjects [redacted] re-initiated deferasinox treatment after temporary interruption due to SF<300 ug/L or LIC<3 mg Fe/g dw liver.

Source: Table 14.2-3.1

Figure 10-4 Box plot of absolute change from baseline for SF values by timepoint



- The length of the box represents the interquartile range (the distance between the 25th and the 75th percentiles), the whiskers extend to the 10th and 90th percentiles, means are presented as dots and medians are connected over time points.
- Baseline is defined as the last available assessment before or on the date of start of study treatment.

Source: Figure 14.2-1.2

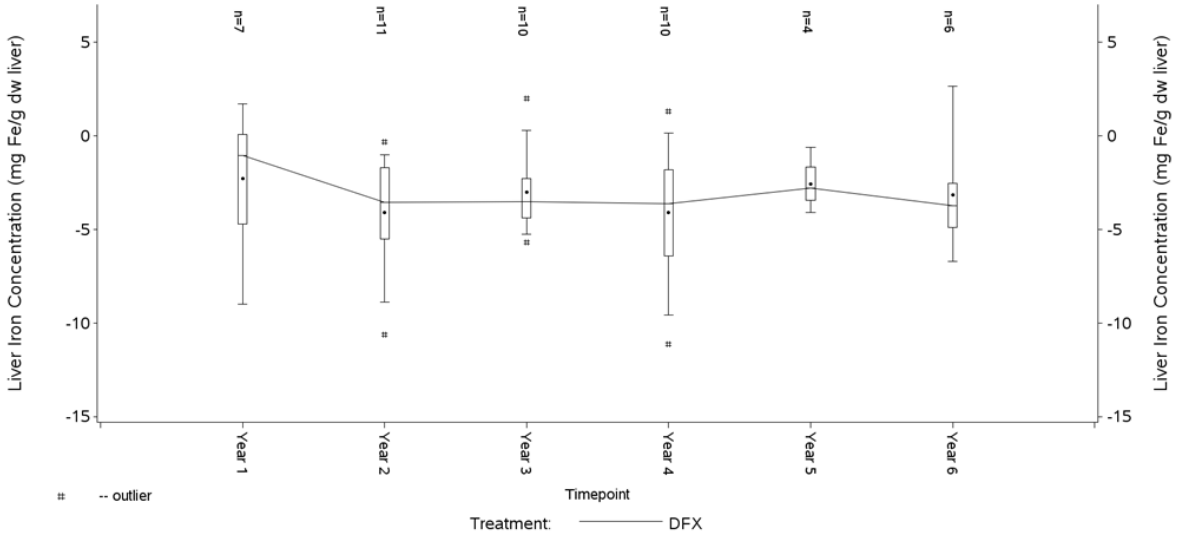
The absolute changes in SF levels from baseline to EOT are represented in Table 14.2-1.1. There was a decrease in the median SF level from baseline to Quarter 20. At baseline, the

median SF level was 801.0 µg/L (Min-Max: 201-2713), with 33 patients. By Quarter 20, the median SF level was 536.3 µg/L with 11 patients.

The absolute and relative changes in LIC levels from baseline to EOT is summarized in Table 14.2-2.1. Baseline and post-baseline data on LIC was limited. There was a decrease in the median LIC level from baseline to Year 5. At baseline, the median LIC level was 8.30 µg/L (Min-Max: 2.70-23.20), with 18 patients. By Year 5, the median LIC level was 3.1620 µg/L with 5 patients.

Some patients received RBC transfusions during the study (Listing 16.2.9-5.1). CMR data are listed in Listing 16.2.9-8.1.

Figure 10-5 Box plot of absolute change from baseline for LIC values by timepoint (FAS)



- The length of the box represents the interquartile range (the distance between the 25th and the 75th percentiles), the whiskers extend to the 10th and 90th percentiles, means are presented as dots and medians are connected over time points.
- Baseline is defined as the last available assessment before or on the date of start of study treatment.

Source: Figure 14.2-1.4

11 Discussion

11.1 Key results

- Overall, 45 patients were enrolled; 26 patients (57.8%) completed the treatment as per protocol and 19 patients (42.2%) discontinued the study. Twenty-one patients were treated with deferasirox DT formulation only, 15 patients switched from DT to FCT, and 9 patients were treated with deferasirox FCT formulation only. The median exposure to deferasirox (regardless of formulation) was 37.52 months (range: 3.2 to 68.7 months). Nineteen patients overall were treated for ≥ 48 months.
- Serum ferritin baseline information was available in 33 (73.3%) patients and LIC baseline information was available in 18 (40.0%) patients, the median values for LIC and SF at

baseline were 8.3 mg Fe/g dw liver (Min-Max: 2.70-23.20), and 801.0 µg/L (Min-Max: 201-2713), respectively.

- Overall, 35(77.8%) patients reported AEs, the most common AEs by PT were upper respiratory tract infection in 9 (20.0%) patients, thrombocytosis, pyrexia, cough, rhinitis, and Vitamin D deficiency in 4 (8.9%) patients each. No patients discontinued the study drug due to AEs.
- Overall, SAEs regardless of study drug relationship were reported in 5 (11.1%) patients which included SAEs by PT of gastroenteritis in 2 (4.4%) patients, portal vein thrombosis, post procedural haemorrhage, influenza and vomiting, in 1 (2.2%) patient each. Vomiting was the only SAE suspected to be study drug related, reported in 1 (2.2%) patient.
- Overall, 9 (20.0%) patients reported AESIs and none of them were study drug related. Hepatic and renal AESIs regardless of study drug relationship, with moderate severity, were reported in 1 patient (2.2%), which included increased ALT and increased blood creatinine. Both events resolved with no action taken to deferasirox treatment.
- ALT, AST and total bilirubin baseline information was available in 37 (82.2%) patients, 35 (77.8%) patients, and 31(68.9%) patients, respectively. No patient in the study had an episode of ALT >5×ULN in at least 2 consecutive post-baseline measurements at least 7 days apart. Despite some missing assessments, no clinically concerning elevations of hepatic enzymes were observed. Most post-baseline values stayed the same or improved.
- One case met Hy's Law criteria but was not considered a DILI case due to confounding factors including medical history of mild hepatic siderosis, infection of Epstein-Barr virus, abnormal liver function assessments at baseline, moderate cholelithiasis 1 day before the biochemical Hy's Law criteria were met.
- Serum creatinine baseline information was available in 37 (82.2%) patients, and CrCl baseline information was available in 27 (60.0%) patients. No concerning decreases in renal function was observed based on SCr and CrCl monitoring. No patient had a notable range (defined as two consecutive values >ULN and >33% increase from baseline) in SCr. No patients met the criteria for notable decreases in CrCl.
- Overall, an increase in weight, height, and BMI from baseline to Quarter 20, was observed. Shift tables on height, weight and BMI SDS showed that majority of patients remained in the same SDS category as at baseline (low or normal). The individual growth curves showed continuous growth in male and female pediatric patients from both age cohorts (10-<=12 and >12-<18) during deferasirox treatment, although growth trends lie within the lower percentiles of US Clinical Growth Charts. These results and conclusions of NESO study are in line with what was observed when the same analysis was conducted in Study CICL670A0107E.
- Limited patient data was available for Tanner stage analyses, with most patients having only 1 to 3 values. Eleven patients had both baseline and post-baseline assessments. One patient exhibited a clinically significant abnormality (delayed puberty) before starting treatment, which persisted throughout the study.
- The long-term efficacy of deferasirox was measured by SF and LIC among 45 patients. The results showed that 19 (42.2%) patients achieved SF levels below 300 µg/L, and 15 (33.3%) patients achieved LIC levels below 3 mg Fe/g dw liver. Additionally, 4 (8.9%)

patients restarted deferasirox treatment after temporary interruption due to SF levels below 300 µg/L or LIC levels below 3 mg Fe/g dw liver.

- Abnormal hematology values were noted in some patients, with most having high or low values prior to treatment or at baseline. Post-baseline, low neutrophils were reported in 9 patients and low platelets in 3 patients.
- Audiometric assessments were documented for 24 patients. Most had post-baseline assessments only. One patient had a clinically significant abnormality (hypoacusis) that was mild and not related to the study treatment. This patient continued treatment until discontinuation due to lack of MRI confirmation of iron overload.
- Ophthalmological examinations were documented for 20 patients. Most had post-baseline assessments only. One patient had a clinically significant ocular abnormality (myopia) prior to treatment, with no post-baseline assessment or ocular AEs reported.
- The results of echocardiograms, ECGs, and vital signs showed no significant abnormalities with the limited data collected.

11.2 Limitations

The limitations of this NIS include missing data at baseline and/or post baseline for some safety and efficacy assessments, due to the lack of a planned visit schedule which lead to variability in data collection.

11.3 Interpretation

The results of this study and their interpretations are presented in Section 10.

12 Conclusion

AEs were commonly reported, while study drug-related AEs were few, most of the AEs were mild to moderate in severity, and no patients discontinued the study drug due to AEs. SAEs were reported in a few patients, vomiting being the only SAE suspected to be study drug-related. All the SAEs were reported to be resolved. Hepatic and renal AESIs, were reported in 1 patient, both of which were not study drug related and were resolved without altering deferasirox treatment.

When analysing growth and development, increases in weight, height, and BMI were observed over five years. Limited data on Tanner stage analyses indicated that most patients had few assessments, with 1 patient reporting delayed puberty before starting treatment, which persisted throughout the study.

The long-term efficacy of deferasirox showed a decreasing trend in SF and LIC, and approximately up to half of patients reaching target levels of SF or LIC post-baseline.

The data was limited, but no significant audiometric and ophthalmological abnormalities were observed while patients were on treatment. Overall, the treatment was well-tolerated. The AEs observed in this study are the expected AEs in the patient population. Few study drug-related AEs were reported, positive growth and development outcomes were observed over the long term. The study highlighted stable renal function and no clinically concerning elevations of

hepatic enzymes, reinforcing the overall positive impact of deferasirox treatment. No new safety signals were identified, and the long-term efficacy and safety of deferasirox remains consistent with its established benefit/risk profile.

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14 Tables, figures and listings referred to but not included in the text

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Appendices

The appendices listed below are based on the ICH study report granulation. Some of the appendices may not be relevant for this report

Appendix 16.1 – Study information

Appendix 16.1.1 - Protocol and protocol amendments

Appendix 16.1.2 - Sample case report form

Appendix 16.1.3 - List of IEC(s) or IRB(s), sample consent form(s)

Appendix 16.1.4 - Information on investigators and other important participants

Appendix 16.1.5 - Signatures

Appendix 16.1.8 - Audit certificates

Appendix 16.1.9 - Documentation of statistical methods

Appendix 16.1.10 - Inter-laboratory standardization methods and QA procedures

Appendix 16.2 – Patient data listings

Appendix 16.2.1 Discontinued patients

Appendix 16.2.2 Protocol deviations

Appendix 16.2.3 Patients excluded from analyses

Appendix 16.2.4 Demographic and other baseline characteristics

Appendix 16.2.5 Compliance-drug concentration data

Appendix 16.2.6 Individual efficacy response data

Appendix 16.2.7 Adverse event listings

Appendix 16.2.8 Listing of individual laboratory measurements

Appendix 16.2.9 Vital signs and other observations related to safety

Appendix 16.3 - Case Report Forms

Appendix 16.4 – Individual patient