27 March 2025
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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Exjade

Deferasirox

Procedure no: EMA/PAM/0000247779

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	19/08/2024	19/08/2024	☐
☐	CHMP Rapporteur Assessment Report	23/09/2024	23/09/2024	☐
☐	CHMP members comments	07/10/2024	07/10/2024	☐
☐	Updated CHMP Rapporteur Assessment Report	10/10/2024	10/10/2024	☐
☐	CHMP adoption of conclusions:	17/10/2024	17/10/2024	☐
☐	Submission	08/11/2024	08/11/2024	☐
☐	Re-start	08/11/2024	08/11/2024	☐
☐	CHMP Rapporteur Assessment Report	27/11/2024	27/11/2024	☐
☐	CHMP members comments	02/12/2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	05/12/2024	n/a	☐
☐	CHMP adoption of conclusions:	12/12/2024	12/12/2024	☐
☐	Submission	28/01/2025	28/01/2025	☐
☐	Re-start	29/01/2025	29/01/2025	☐
☐	CHMP Rapporteur Assessment Report	12/02/2025	12/02/2025	☐
☐	CHMP members comments	17/02/2025	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	20/02/2025	20/02/2025	☐
☐	CHMP adoption of conclusions:	27/02/2025	27/02/2025	☐
☐	Submission	04/03/2025	04/03/2025	☐
☐	Re-start	05/03/2025	05/03/2025	☐
☐	CHMP Rapporteur Assessment Report	12/03/2025	12/03/2025	☐
☐	CHMP members comments	17/03/2025	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	20/03/2025	n/a	☐
☒	CHMP adoption of conclusions:	27/03/2025	27/03/2025	☐

Table of contents

1. Introduction

On 11 July 2024, the MAH submitted a completed paediatric study for deferasirox (Exjade), in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Deferasirox (DFX) is currently marketed under the brand name Exjade and approved for the treatment of:

- chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients with beta-thalassemia aged 6 years and older, and when deferoxamine therapy is contraindicated or inadequate in patients aged 2 years and older (until 5 years for beta-thalassemia major).
- non-transfusion dependent thalassemia syndromes in patients aged 10 years and older, and
- other type of anaemia in patients aged 2 and older.

Two pharmaceutical formulations of Exjade exist, both approved for paediatric administration:

- 90 mg, 180 mg and 360 mg film-coated tablets
- 90 mg, 180 mg and 360 mg granules in sachets

Since 1st March 2021, 125 mg, 250 mg and 500 mg dispersible tablets (DT) are no longer marketed in the EU/EEA countries.

The MAH stated that Study CICL670F2202 (hereafter referred as F2202) is part of the clinical development program, generating additional safety data for the granule formulation.

2.2. Information on the pharmaceutical formulation used in the study

The granule formulation was initially developed to offer an alternative to paediatric patients using the DT formulation, authorized in August 2006. Granules in sachets were granted marketing authorization in November 2017. For this formulation, the active substance (DFX) has been strength-adjusted to achieve comparable exposure to the DT formulation and several excipients have been modified.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for Study F2202 entitled 'A randomized, open-label, multicenter, two-arm, phase II study to evaluate treatment compliance, efficacy and safety of an improved deferasirox formulation (granules) in paediatric patients with iron overload'.

2.3.2. Clinical study

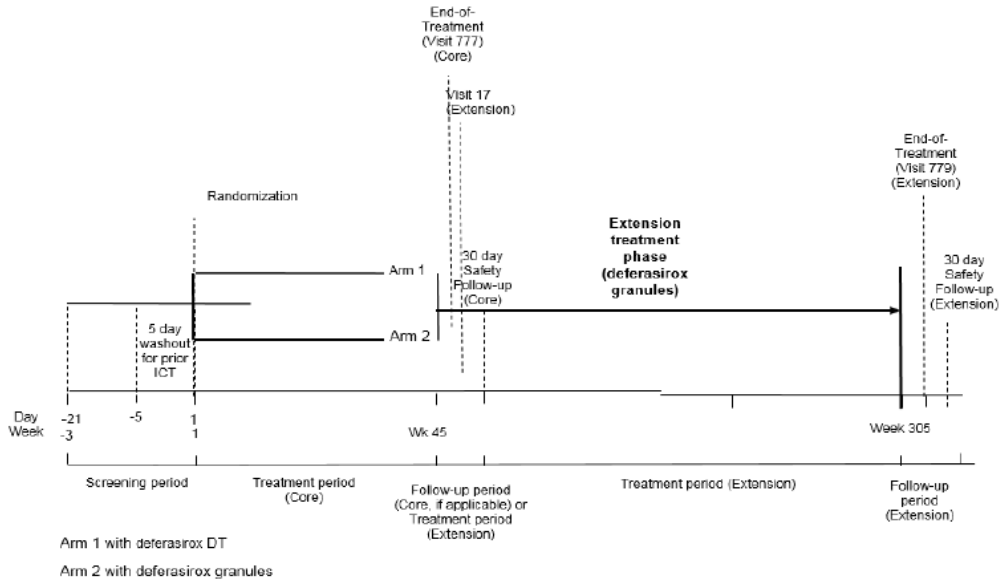
Study F2202

Description

Study F2202 was a randomized, open-label, multicenter, two arm, Phase II study to evaluate safety and treatment compliance with a deferasirox granule formulation versus a deferasirox DT formulation in children and adolescents aged ≥ 2 and <18 years at enrolment with any transfusion-dependent anaemia requiring chelation therapy due to iron overload, and having a treatment goal to reduce iron burden as measured by serum ferritin (SF).

Study period: 21-Oct-2015 (first subject first patient) to 15-Jan-2024 (last subject last visit)

Figure 1. Study design



Upon confirmation of eligibility for study by the Investigator, subjects previously treated with iron-chelation therapy (ICT) underwent a 5-day chelation washout period.

All subjects were then randomly assigned in ratio of 1:1 to either Deferasirox DT (Arm 1) or granules (Arm 2). Randomization was stratified by age groups (2 to <10 years, 10 to <18 years) and by prior ICT (Yes/No).

Randomized subjects were treated with either DFX DT or granules for a 48-week treatment period, followed by an optional extension phase during with they received the granules up to 5 years. Those who demonstrated benefit to granules or DT in the core phase, and/or expressed the wish to continue in the optional extension phase on granules, were offered this possibility until there is local access to the new formulation (granules or film-coated tablets [FCT]) or up to 5 years entering extension phase, whichever occurs first.

Methods

Study participants

Up to 216 ICT naive and pre-treated (96 ICT naive and up to 120 pre-treated) male and female children and adolescents aged ≥ 2 and <18 years at enrolment with any transfusion-dependent anaemia requiring chelation therapy due to iron overload, and a treatment goal to reduce iron burden were to be included in this study. At least 96 subjects (48 per treatment arm) were to be ICT-naive.

Treatments

Study participants received either:

- DFX DT 20 mg/kg once daily (Arm 1) on an empty stomach and at least 30 minutes before the next meal in an appropriate amount of water, apple juice or orange juice or;
- DFX granules 14 mg/kg once daily (Arm 2) on an empty stomach or with a light meal, sprinkled on a soft food.

For each patient the daily dose was calculated by the physician based on the patient's actual body weight, and then rounded up or down to the nearest whole tablet/stick pack according to the available strengths of deferasirox formulations (125 mg, 250 mg and 500 mg for the DT and 90 mg, 180 mg and 360 mg for the granules).

Dose adjustment for better treatment effects in steps of 5-10 mg/kg/day for deferasirox DT or in steps of 3.5-7.0 mg/kg/day for deferasirox granules based on serum ferritin levels and investigator's judgment can be considered every 3 months after starting the study treatment.

Dose adjustments based on safety was allowed at any time point in the study. The maximum dose of deferasirox DT was 40 mg/kg/day and the maximum dose of deferasirox granules was 28 mg/kg/day.

The starting dose and the dose adjustment considerations must take into account that the therapeutic goal is reduction of iron burden (as opposed to maintenance of iron burden).

Objectives and endpoints

Table 1. Study objectives and endpoints

Objectives	**Endpoints**
Primary	
To evaluate both formulations on subject compliance, using stick pack/tablet count 24 weeks of treatment in ICT-naïve subjects during core phase	Compliance measured by stick pack/tablet count over 24 weeks of treatment
To evaluate the change from Baseline in serum ferritin after 24 weeks of treatment for both formulations in ICT-naïve subjects during the core phase	Change from baseline in serum ferritin after 24 weeks of treatment (i.e. serum ferritin at week 25 visit)
Secondary	
To evaluate both formulations on change in serum ferritin and compliance in ICT-naïve subjects, after 48 weeks of treatment	Compliance measured by stick pack/tablet count after 48 weeks of treatment Change from baseline in serum ferritin after 48 weeks of treatment

To evaluate both formulations on change in serum ferritin after 24 weeks and 48 weeks of treatment in ICT-naïve and pre-treated subjects	Change from baseline in serum ferritin after 24 weeks (i.e. assessed at week 25) and 48 weeks of treatment
To evaluate both formations on subject satisfaction and palatability using Patient/Observer Reported Outcomes (PRO/ObsRO) questionnaires	Domain scores of treatment satisfaction and palatability over time
To evaluate both formulations on overall safety	Overall safety, as measured by frequency and severity of adverse events (including active monitoring for renal toxicity; renal failure, hepatic toxicity; hepatic failure, and gastrointestinal haemorrhage), and changes in laboratory values from baseline (serum creatinine, creatinine clearance, ALT, AST, RBC and WBC). In addition, vital signs, physical, ophthalmological, audiometric, cardiac, and growth and development evaluations were assessed.
To evaluation compliance using a daily PRO/ObsRO questionnaire	Rate of dosing instruction deviations (doses missed/not taken at the same time every day)
To evaluate pre-dose PK data to support the assessment of compliance	Pre-dose deferasirox concentrations in all subjects [except Egypt] at Weeks 1, 3, 5, 9, 13, 17, 21, 25, 29; 33, 41 and 45 visits (13 samples)
Post-dose data to be analysed along with pre-dose PK data	Post-dose deferasirox concentrations between 2 and 4 hours post-dose at Weeks 5 and 9 (2 samples)
To explore exposure-relationships for measures of safety and effectiveness	Serum creatinine change from baseline, notable serum creatinine event, serum creatinine clearance change from baseline and notable serum creatinine clearance events, urine protein creatinine ratio change from baseline and serum ferritin change from baseline, in relationship to pre- and post-dose DFX concentrations
Secondary (optional extension phase)	
To assess additional safety data about new formulation (granules) in paediatric population	Overall safety, as measured by frequency and severity of adverse events (including active monitoring for renal toxicity; renal failure, hepatic toxicity; hepatic failure, and gastrointestinal haemorrhage), and changes in laboratory values from baseline (serum creatinine, creatinine clearance, ALT, AST, RBC and WBC). In addition, vital signs, physical, ophthalmological, audiometric, cardiac, and growth and development evaluations were assessed.

Randomisation and blinding (masking)

Randomisation

During the core phase, all subjects who fulfilled all inclusion/exclusion criteria were randomized via Interactive Response Technology (IRT) to either DFX DT or granules. Randomization was stratified by age groups (2 to <10 years, 10 to <18 years) and by prior ICT (Yes/No).

During the optional extension phase, all subjects were provided with DFX granules. No randomization was performed.

Blinding

Not applicable for this open-label study.

Statistical Methods

The table below summarizes the efficacy analyses performed in the following sets of the study population:

- Full analysis set 1 (FAS-1): ICT-naive subjects (N=108);
- Full analysis set 2 (FAS-2): subjects pre-treated with ICT (N=116);
- Full analysis set 3 (FAS-3): all randomized subjects (ICT-naive and ICT pre-treated subjects, N=224);
- Safety set-4: all subjects who received at least 1 dose of granule formulation during the core or extension phase (N=179). The subjects in the extension phase received granules regardless of which arm they were initially randomized (110 subjects initially randomized into the granules arm and 69 subjects who were initially randomized into the DT arm and crossed over to the granules arm during the extension phase).

Table 2. Efficacy analyses of Study F2202

Efficacy endpoints	**Method of analysis**
Primary	
Subject compliance up to 24 weeks of treatment in FAS-1 (ICT-naive subjects)	The hypothesis testing was done at the primary analysis. An analysis of covariance (ANCOVA) was used for comparison between both treatment groups and included treatment group and the age group as per stratification (2 to <10 years vs. 10 to <18 years), as factors. The following estimates from the ANCOVA were provided: - the least squares mean with 2-sided 95% confidence interval for each treatment arm - the least squares means with 2-sided 95% confidence interval, p-value for the difference between treatment arms
Change from baseline in serum ferritin (SF) up to 24 weeks of treatment in FAS-1	There was no formal hypothesis testing at the EOC phase analysis, and no p-values were generated. An ANCOVA was performed for comparison between both treatment groups. The ANCOVA model for SF included the same factors as the ANCOVA model for compliance endpoint and the baseline SF value as a covariate.
Secondary	

Compliance up to 48 weeks of treatment in FAS-1, FAS-2 (ICT pre-treated subjects), and FAS-3 (all subjects)	Summary statistics of overall compliance and 95% CIs for means were provided.
Change from baseline in SF up to 24 weeks of treatment in FAS-2 and FAS-3	Summary of absolute and relative change from baseline values and 95% CIs for means were provided.
Change from baseline in SF up to 48 weeks of treatment in FAS-1, FAS-2, and FAS-3	Summary of absolute and relative change from baseline values and 95% CIs for means were provided.
Change from baseline in SF at every year visit during the entire granule period in safety set-4	Summary of absolute and relative change from baseline values and 95% CIs for means were provided.
Patient reported outcomes/Observer reported outcomes (PRO/ObsRO) in FAS-1, FAS-2, and FAS-3	Three questionnaires were used: the modified Satisfaction with Iron Chelation Therapy (mSICT), a palatability questionnaire and a compliance diary. Standard descriptive statistics were provided.

Assessor's comment:

Study F2022 aimed to evaluate the efficacy and safety of DFX granule formulation compared to DFX dispersible tablets in paediatric subjects with iron overload. The weight-adjusted dosing paradigm for DFX granules was consistent with the development of Exjade dispersible tablets. Treatment compliance was measured by stick pack/tablet count and efficacy results were measured by change from baseline in SF. Secondary efficacy objectives were assessed using similar endpoints, except for patient or observer reported outcomes (PRO/ObsRO) that were assessed using questionnaires (i.e. a satisfaction questionnaire, a palatability questionnaire and a compliance diary).

Proposed objectives, endpoints and the corresponding statistical were considered acceptable when data from the end of the core phase (data cut-off: 21-Jan-2021) were analysed as part of the assessment of Exjade procedure No. EMEA/H/C/000670/II/0082/G.

Assessment of the current P46 procedure (data cut-off: 15-Jan-2024) will mainly focus on the safety set- (i.e. all subjects who received at least 1 dose of granule formulation during the core or extension phase, N=179) to further characterize the longer-term safety profile of the granule formulation.

Results

Participant flow

A total of 224 subjects were randomized over 17 countries.

Recruitment

Inclusion criteria

1. Written informed consent/assent before any study-specific procedures.
2. For core phase only: Male and female children and adolescents aged ≥ 2 and <18 years. [France: Male and female children and adolescent aged ≥ 2 and <18 years old, however children aged ≥ 2 and ≤ 6 years were to be enrolled only when deferoxamine treatment was contraindicated or inadequate in these subjects as per Investigator decision]. The subjects who turned 18 years in the core phase, were considered eligible for participation in the optional extension phase as well.

3. Any transfusion-dependent anaemia associated with iron overload requiring ICT and with a history of transfusion of approximately 20 packed red blood cells (PRBC) units and a treatment goal to reduce iron burden (300 mL PRBC = 1 unit in adults whereas 4 mL/kg PRBC was considered 1 unit for children).

4. Serum ferritin >1000 ng/mL, measured at screening Visit 1 and screening Visit 2 (the mean was used for eligibility criteria).

For optional extension phase eligibility only

5. Subject had to participate and complete the 48-weeks core phase treatment as per protocol.

Exclusion criteria

1. Creatinine clearance below the contraindication limit in the locally approved prescribing information (using Schwartz formula) at screening visit 1 or screening visit 2.

2. Serum creatinine >1.5×upper limit normal (ULN) at screening Visit 1 or screening Visit 2.

3. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >3.0×ULN and Direct (conjugated) bilirubin >2×ULN at screening Visit 1 or screening Visit 2.

4. Liver disease with severity of Child-Pugh class B or C.

5. Significant proteinuria as indicated by a urinary protein/creatinine ratio >0.5 mg/mg in a second morning urine sample at screening Visit 1 or screening Visit 2.

6. Subjects with significant impaired gastrointestinal (GI) function or GI disease that might significantly alter the absorption of oral deferasirox (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhoea, malabsorption syndrome, or small bowel resection).

7. Clinical or laboratory evidence of active Hepatitis B or Hepatitis C (HBsAg (hepatitis B virus) in the absence of HBsAb OR hepatitis C virus (HCV) Ab positive with HCV RNA (ribonucleic acid) positive).

8. Subjects with psychiatric or addictive disorders which prevent them from giving their informed consent or undergoing any of the treatment options or subjects unwilling or unable to comply with the protocol.

9. Subjects with a known history of Human immunodeficiency virus (HIV) seropositivity (Elisa or Western blot).

10. History of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell or squamous cell carcinoma of the skin.

11. Subjects participating in another clinical trial or receiving an investigational drug.

12. History of hypersensitivity to any of the study drug or excipients.

13. Significant medical condition interfering with the ability to partake in this study e.g. systemic uncontrolled hypertension, unstable cardiac disease not controlled by standard medical therapy, systemic disease (cardiovascular, renal, hepatic, etc.).

14. Female subjects of childbearing potential (e.g. are menstruating) who did not agree to abstinence or, if sexually active, did not agree to the use of contraception as defined in Appendix 16.1.1-Protocol-Section 7.2.4.5.4.

15. For prohibited medication please refer to Appendix 16.1.1-Protocol-Section 6.3.2.

16. Pregnant or nursing (lactating) women
17. Direct (conjugated) bilirubin >2 x ULN at screening visit 1 or screening visit 2.
18. History or current diagnosis of cardiac disease indicating significant risk of safety for subjects participating in the study such as uncontrolled or significant cardiac disease, including any of the following: clinically significant (symptomatic) cardiac arrhythmias (e.g., sustained ventricular tachycardia, and clinically significant second or third degree atrioventricular block (AV) block without a pacemaker).

For optional extension phase eligibility only

19. Local access to new formulation (granules or FCT) was available.

Protocol amendments

The study protocol was amended 6 times. The original protocol and all amendments are provided in Appendix 16.1.1. The key features of each amendment are given in the table below.

Table 3. Summary of key protocol changes

Version and date	**Summary of key changes**
Amendment 1 (01-De-2015)	• Expansion of the study population by revising the inclusion criteria to allow for the enrolment of up to 120 subjects who had prior history of ICT in addition to the 120 ICT-naive subjects originally planned. • Modification of the secondary objectives: - Revised sparse PK sampling schedule to reduce required blood draws and extensive/overnight hospital stays in this paediatric population to improve feasibility of study. - Addition of new objective to evaluate the change in SF in both populations (ICT naive and ICT pre-treated subjects). - In order to optimize the subject safety and the toxicity monitoring (including renal and hepatic monitoring), eligibility criteria and the management guidelines for cardiac and hepatic toxicity were revised. - Statistical methods and data analysis section was updated in alignment with the updated PK sampling and the inclusion of ICT pre-treated subjects.
Amendment 2 (15-Jun-2016)	• To allow the sites in Egypt to use a local laboratory instead of central laboratory for the analysis of safety and to exempt subjects enrolled in Egypt from the collection of PK samples. This exemption was granted due to national restriction on export of any biological samples out of Egypt. • To clarify the inclusion criteria #2 for France concerning children aged from 2 to 6 years old as per Exjade PI.
Amendment 3 (24-Aug-2016)	• Addition of an optional extension phase to the existing study allowed the subjects who participated and completed the 48-weeks core treatment phase as per protocol, and did not have access to the new formulation (granules or FCT), the possibility to extend treatment with deferasirox granules for a maximum of 5 years after completing the core treatment phase or until there was local access to new formulation (granules or FCT), whichever occurred first. Subjects only who demonstrated benefit to granules or DT in the core phase, and/or expressed the wish to continue in the optional extension phase on granules were started in the optional extension phase.

	• To clarify the eligibility criteria related to renal criteria to promote better Investigator understanding, for better adherence and improved renal safety. • To provide Investigators with further clarified dose modification guidance for renal monitoring with regards to creatinine clearance, increased serum creatinine and proteinuria. Clear guidance on how to reinitiate treatment after required dose interruption was also included.
Amendment 4 (15-Jun-2017)	• An IA to allow for early analysis of the data if requested by the health authority. • Allow for paper PRO use and completion, in case of technical issue or malfunctioning of the electronic device and • Clarify various points to improve site understanding and consistency in implementation of the protocol.
Amendment 5 (06-Dec-2017)	• To modify the assessment time-point for the primary analysis (from change from Baseline for SF and compliance after 48-weeks of treatment to after 24-weeks). A linear relationship between changes from Baseline at 24 and 48-weeks of treatment was established based on a pool of representative randomized studies (CICL670A0105, CICL670A0107, CICL670A0109 and CICL670A2206) with SF available at 6 and 12-months for deferoxamine and deferasirox arms. This finding supported the use of the 6-month time-point as reliable surrogate for the 12-month time-point (Novartis data on file). Primary endpoints based on changes from Baseline after 24-weeks of treatment allowed an earlier disclosure of primary analysis. The compliance (using drug count) was evaluated in pediatric subjects over 6 months and 12 months for deferoxamine and deferasirox arms in the study ICL670A2206. The observed treatment effect over 6 months vs. 12 months was similar. This suggested compliance over 6 months was accurate at predicting compliance over 12 months. Furthermore, data comparing deferoxamine and deferasirox suggested a self-reported adherence to deferasirox DT of 97% after one year. Therefore, it can be assumed that the 6-month reported adherence would be very similar and would serve as a surrogate. The rationale was also based on the demonstrated relationship of efficacy as assessed by SF with deferasirox dose, iron burden and continuous iron intake. • To reduce the sample size for the ICT naive subjects, following interactions with Health Authorities as the recruitment of ICT naive subjects was much slower than anticipated due to the global availability of chelation therapies in these indications. It was discussed and agreed that the sample size for ICT naïve subjects would be reduced to reflect the modification of primary endpoints. At least 96 ICT naive subjects were planned to be enrolled instead of 120 subjects. This lower sample size would allow to obtain 76% power at a one-sided 5% level of significance for showing superiority of granule formulation over DT formulation with respect to change from Baseline after 24-weeks of treatment in SF, assuming a dropout rate of 5%. This power was considered adequate to demonstrate targeted treatment effect, and would allow an earlier full recruitment of ICT naive subjects in the study, and therefore an earlier disclosure of primary analysis. • The eligibility criteria for the extension phase were modified to allow subjects who participated and completed 48-weeks of treatment in the core phase and for whom new formulation was not available to continue in the extension phase, if they derived clinical benefit from the study drug, as confirmed by Investigator. The prior criteria were too stringent and would unnecessarily exclude subjects who were benefiting from

	the study drug. During the extension phase, subjects would continue to follow the protocol including any dose modification guidelines and early withdrawal/discontinuation guidelines as they did in the core phase of the study.
Amendment 6 (26-Jun-2021)	• The main purpose of this amendment was to introduce the requirement for central collection and assessment of photographs from ocular examinations (lens photographs and wide angle fundus photographs) collected during the study by a Novartis designated imaging Contract Research Organization (CRO). This change was in response to a Health Authority request to submit CALYPSO ophthalmic data (for up to 2 years of follow up) to support the ocular safety evaluation of deferasirox. • Clarification was also added to state that for patients who need correction, the best corrected visual acuity should be tested when performing the distance visual acuity test and that the corrected visual acuity should be documented in the source records. • In addition, mitigation procedures were implemented throughout the protocol to ensure participant safety and trial integrity during a Public Health emergency, as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster. Public health emergency mitigation guidelines, regarding the use of a local laboratory if the subject was unable to conduct safety laboratory assessments at the site was included. • Finally, assessment of the study Risk/Benefit in light of the ongoing coronavirus disease 2019 (COVID-19) pandemic at the time of this protocol amendment concluded that there are no additional risks related to COVID-19 for this study. Patients with cytopenias are more susceptible to infections in general, compared to patients without cytopenias. There have been postmarketing reports of cytopenias in patients treated with deferasirox and patients with cytopenias may be at higher risk of COVID-19 with a poorer prognosis. The periodic monitoring of blood counts and interruption of study treatment in patients who develop unexplained cytopenia, as defined in the protocol, are expected to mitigate this risk.

Assessor's comment:

Eligibility criteria are consistent with the study objectives and endpoints.

Concerning protocol amendments, no changes to protocol have been made since the last data cut-off on 26 January 2021. Main changes include improved patient safety, updated dose modification guidance, monitoring of relevant safety parameters (e.g. for renal or ocular toxicity), adaptation of the study endpoints and adaptation of sample size based on accumulated post-marketing data and following feedback from competent Health Authorities. An open-label extension phase has been also added by protocol amendment 3 to collect longer-term efficacy and safety data with the granule formulation. None of those changes are considered to have had an impact on study conduct.

Baseline data

Demographics and baseline disease characteristics

The demographics and baseline disease characteristics for all randomized subjects at the study start were detailed in Study F2202 primary CSR-Section 11.

An additional table was generated for Baseline characteristics for the 179 subjects in Safety Set-4, hence the height and weight for the subjects in the cross-over group at Baseline are different, but the age and

age categories remain the same as reported in the primary CSR (start date of granules treatment is taken as 'Baseline' value in cross-over group for height and weight).

Demographics

The median age of subjects was 5 years (range: 2 to 16 years) with the majority (83.8%) of subjects belonging to 2 - <10 years of age category. The study population was predominantly of White (48.6%) or Asian (39.1%) race. The gender proportion was similar in both the treatment groups (see table below).

Table 4. Demographics (Safety Set-4)

Demographic variable	DFX Cross-over N=69	DFX Granule N=110	All patients N=179
Age (years)			
n	69	110	179
Mean (SD)	5.7 (3.97)	5.9 (3.91)	5.8 (3.92)
Median	5.0	4.5	5.0
Q1-Q3	2.0-8.0	2.0-9.0	2.0-9.0
Min-Max	2-16	2-15	2-16
Age category-n (%)			
2-<10 Years	61 (88.4)	89 (80.9)	150 (83.8)
10-<18 Years	8 (11.6)	21 (19.1)	29 (16.2)
Sex-n (%)			
Female	34 (49.3)	55 (50.0)	89 (49.7)
Male	35 (50.7)	55 (50.0)	90 (50.3)
Race-n (%)			
White	36 (52.2)	51 (46.4)	87 (48.6)
Asian	27 (39.1)	43 (39.1)	70 (39.1)
Black Or African American	2 (2.9)	8 (7.3)	10 (5.6)
Other	4 (5.8)	8 (7.3)	12 (6.7)
Ethnicity-n (%)			
Other	66 (95.7)	98 (89.1)	164 (91.6)
Hispanic/Latino	0 (0.0)	6 (5.5)	6 (3.4)
Chinese	0 (0.0)	3 (2.7)	3 (1.7)
Indian (Indian Subcontinent)	2 (2.9)	2 (1.8)	4 (2.2)
Mixed Ethnicity	1 (1.4)	1 (0.9)	2 (1.1)

Weight (kg)			
n	68	110	178
Mean (SD)	22.19 (12.892)	21.35 (11.482)	21.67 (12.011)
Median	18.25	16.70	17.50
Q1-Q3	13.90-23.95	12.90-25.00	13.60-25.00
Min-Max	10.8-84.5	9.7-64.3	9.7-84.5
Weight category (kg)-n (%)			
< 20	37 (53.6)	65 (59.1)	102 (57.0)
20 - <35	24 (34.8)	27 (24.5)	51 (28.5)
35 - <55	4 (5.8)	16 (14.5)	20 (11.2)
55 - <75	2 (2.9)	2 (1.8)	4 (2.2)
>= 75	1 (1.4)	0 (0.0)	1 (0.6)
Height (cm)			
n	68	110	178
Mean (SD)	114.37 (21.550)	110.84 (21.851)	112.19 (21.743)
Median	110.00	106.75	108.05
Q1-Q3	97.00-126.00	92.00-127.00	95.00-127.00
Min-Max	87.0-181.0	75.0-159.0	75.0-181.0

Race reported in eCRF as "Caucasian" or "Black" corresponds to the reported category "White" or "Black or African American", respectively.

For Age and Age category Baseline is defined as the last non-missing value prior or on the day of first dose of randomized treatment.

For Weight and Height, the last available value before or on start date of granules treatment is taken as 'Baseline' value in DFX Cross-over group. Baseline is defined as the last non-missing value prior or on the day of first dose in DFX granule group.

Source: Table 14.1-8.4

Baseline disease characteristics

Table 5. Disease characteristics by treatment (Safety Set 4)

Disease characteristics	DFX Cross-over N=69 n (%)	DFX Granule N=110 n (%)	All patients N=179 n (%)
Main underlying disease-n (%)			
Beta-thalassemia major	48 (69.6)	65 (59.1)	113 (63.1)
Haemoglobin E-disorder	11 (15.9)	12 (10.9)	23 (12.8)
Other	3 (4.3)	13 (11.8)	16 (8.9)
Sickle cell	2 (2.9)	12 (10.9)	14 (7.8)
Hemolytic anemia	3 (4.3)	3 (2.7)	6 (3.4)
Beta-thalassemia intermedia	1 (1.4)	1 (0.9)	2 (1.1)
Diamond-blackfan anemia	0	2 (1.8)	2 (1.1)
Franconi's anemia	0	1 (0.9)	1 (0.6)
Red cell aplasia	1 (1.4)	0	1 (0.6)
Sideroblastic anemia	0	1 (0.9)	1 (0.6)
Time since diagnosis (years)			
n	69	110	179
Mean	5.0466	4.6138	4.7807
SD	3.97982	3.62006	3.75770
Median	3.2334	3.4771	3.3840
Minimum	0.370	0.005	0.005
Maximum	16.025	13.854	16.025
Prior ICT-n (%)			
Yes	36 (52.2)	58 (52.7)	94 (52.5)
No	33 (47.8)	52 (47.3)	85 (47.5)

Deferasirox prior to study drug-n (%)*			
Yes	20 (29.0)	42 (38.2)	62 (34.6)
No	16 (23.2)	16 (14.5)	32 (17.9)
Last ICT received-n (%)			
Deferoxamine (DFO)	11 (15.9)	12 (10.9)	23 (12.8)
Deferiprone (DFP)	6 (8.7)	3 (2.7)	9 (5.0)
combination Of Dfo/Dfp-Dfp	3 (4.3)	6 (5.5)	9 (5.0)
Deferasirox (DFX)	12 (17.4)	28 (25.5)	40 (22.3)
combination Of Dfo/Dfx-Dfx	1 (1.4)	4 (3.6)	5 (2.8)
combination Of Dfx/Dfp-Dfp	3 (4.3)	5 (4.5)	8 (4.5)
Time since last ICT (years)			
n	36	58	94
Mean	2.0499	1.9217	1.9708
SD	2.24983	2.16878	2.18900
Median	1.3566	0.9870	1.0897
Minimum	0.022	0.044	0.022
Maximum	8.433	8.561	8.561
Total number of transfusions received			
n	63	102	165
Mean	71.7	66.9	68.7
SD	96.84	99.07	97.96
Median	37.0	31.0	32.0
Minimum	20	4	4
Maximum	593	712	712
History of splenectomy-n (%)			
Yes	1 (1.4)	5 (4.5)	6 (3.4)
No	68 (98.6)	105 (95.5)	173 (96.6)
Hepatitis status-n (%)			
Hepatitis B	2 (2.9)	1 (0.9)	3 (1.7)
No hepatitis	67 (97.1)	109 (99.1)	176 (98.3)

***Assessor's comment*:**

The previous reports presented the primary analysis and the end of core phase results based on full analysis sets (FAS-1, FAS-2, and FAS-3) and the relevant safety sets (Safety Set-1, Safety Set-2 and Safety Set-3).

Safety Set-4 was introduced to capture data of two distinct treatment groups: one group including data from the start of the randomized treatment (granule group) and the other included only a sub-set of the DT group after subjects entered the extension phase to receive granules (cross-over group), with a shorter follow-up.

Although the table format presented above and in the subsequent sections below is with both groups side by side, the treatment groups cannot be compared and need to be interpreted based on the different treatment periods they represent.

As of 15 January 2024, 179 patients received at least one dose of DFX granule formulation, 110 of whom were allocated to this formulation during the core phase. The remaining 69 patients switched to granules after 24 weeks of treatment with dispersible tablets. Consistently with previous assessment, demographics were well-balanced in terms of sex, weight and height, with a median age of 5 years for both groups. Most patients who switched to the granule formulation were between 2 and 10 years old.

Regarding baseline disease characteristics, most patients had beta thalassemia major: 48 patients in the cross-over group vs. 65 patients in the granule group (59.1%), followed by haemoglobin E-disorder (11 [15.9%] and 12 patients [10.9%], respectively) and sickle cell disease for the DFX granule group only (13 patients, 11.8%).

In both groups, median time since diagnosis was around 3 years, with a similar proportion of patients with previous ICT (52.5% and 52.7%), the last ICT received mostly being deferasirox alone (17.4% and 25.5%) or deferoxamine (15.9% and 10.9%).

Prior and concomitant therapy

Prior therapy

Please refer to the table above and final CSR for more details.

Concomitant therapy

As shown in final CSR, 93.6% subjects in the granules group during the core or extension phase received a concomitant medication. The concomitant medications that were used in ≥ 10% of the subjects were: paracetamol (64.5%), amoxi-clavulanico (30.9%), ibuprofen (20.9%), influenza vaccine (15.5%), amoxicillin (15.5%), salbutamol (14.5%), cetirizine (12.7%), cetirizine hydrochloride (12.7%), azithromycin (10.9%) and carbocisteine (10.9%)

In the cross-over group during the extension phase, 91.3% subjects received a concomitant medication. The concomitant medications that were used in ≥ 10% of the subjects were: paracetamol (65.2%), ibuprofen (21.7%), amoxi-clavulanico (20.3%), sodium chloride (17.4%), amoxicillin (14.5%), azithromycin (14.5%), influenza vaccine (14.5%), dextrose and sodium chloride injection (14.5%), other viral vaccines (13.0%), chlorphenamine (13.0%), carbocisteine (11.6%), cefuroxime (10.1%), cetirizine (10.1%), omeprazole (10.1%) and folic acid (10.1%).

***Assessor's comment*:**

Transfusions and concomitant medications were allowed during study, which ensured patient safety. As of 25 January 2024, over 90% of subjects received concomitant medications in both treatment arms. Sixty-two of the 179 subjects (34.6%) had received prior deferasirox therapy at any time before the study enrolment and 40 subjects (22.3%) received deferasirox as the last ICT at any time before study enrolment.

Use of analgesics and anti-infective drugs was overall similar between the two groups, regardless of the initial treatment arm.

Number analysed

Analysis sets

Table 6. Analysis set of core phase (FAS-3)

Analysis set	DFX DT N=112 n (%)	DFX Granule N=112 n (%)	All patients N=224 n (%)
Full analysis set 3	112 (100.0)	112 (100.0)	224 (100.0)
Safety set-3#	111 (99.1)	110 (98.2)	221 (98.7)
Safety set-1	54 (48.2)	52 (46.4)	106 (47.3)
Safety set-2	57 (50.9)	58 (51.8)	115 (51.3)

Three subjects were randomized and not treated

N is the number of patients in FAS-3.

Full Analysis Set 3 (overall population of ICT-naive and ICT-pre-treated subjects) was used only for the analysis of SF values (final CSR, Section 11.1)

The Safety Set 1 (all ICT naive subjects who received at least one dose of the study drug during the core phase, N=106), Safety Set 2 (all ICT pre-treated subjects who received at least one dose of study drug during the core phase, N=115) and Safety Set-3 (all subjects who received at least one dose of study drug during the core phase, N=221) were used only for the analysis of lens photography (LOCSIII) and

color fundus photography. Both assessments were only collected since Protocol Amendment 6 which was implemented after the EoC CSR, (see table above, and final CSR, Section 12.6.2.5).

Table 7. Analysis set of the entire granule period (Safety Set-4)

Analysis set	DFX Cross-over N=69 n (%)	DFX Granule N=110 n (%)	All subjects N=179 n (%)
Safety set-4	69 (100.0)	110 (100.0)	179 (100.0)

N is the number of subjects in Safety Set-4.
Source: Table 14.1-4.2

Safety Set-4 (N=179) consisted of all subjects who received at least 1 dose of granule formulation during the core or extension phase with 110 subjects initially randomized in the granules group and 69 subjects initially randomized in the DT group who crossed over to receive granules in the extension phase (see table above).

***Assessor's comment*:**

The following analysis sets are considered relevant for this assessment:

- the full analysis set 3 (FAS-3), including ICT-naïve and ICT-pre-treated subjects as of 26 January 2021 was used for the analysis of SF values;
- the safety set-3 (all subjects who received at least one of study during core phase, N=221) used for ocular examinations;
- the safety Set-4 (N=179) represented the long-term safety follow-up data (up to 6 years) of the deferasirox new granule formulation in the core and extension phase for subjects randomized to granules (granules group) and the extension phase only for subjects who crossed-over from DT to granules (cross-over group).

Efficacy results

Patient disposition

Table 8. Subject disposition during the extension phase (Safety Set-4)

	DFX Cross-over N = 69 n (%)	DFX Granule N = 110 n (%)	All Subjects N = 179 n (%)
Subject entered in the optional extension phase (M)	69 (100)	77# (70.0)	146# (81.6)
Completed extension phase	42 (60.9)	46 (59.7)	88 (60.3)
Discontinued from extension phase	27 (39.1)	31 (40.3)	58 (39.7)
Reason for discontinuation			
Adverse event	3 (4.3)	9 (11.7)	12 (8.2)
Physician decision	6 (8.7)	8 (10.4)	14 (9.6)
Withdrawal by parent/guardian	10 (14.5)	7 (9.1)	17 (11.6)
Lack of efficacy	2 (2.9)	3 (3.9)	5 (3.4)
Withdrawal by subject	2 (2.9)	2 (2.6)	4 (2.7)
Protocol deviation	0	1 (1.3)	1 (0.7)
Recovery	1 (1.4)	1 (1.3)	2 (1.4)

Death	1 (1.4)	0	1 (0.7)
Technical problems	2 (2.9)	0	2 (1.4)

The percentages for first row are based on N and subsequent rows are based on M.

One additional subject entered the extension phase but was not treated

Adverse events leading to study treatment discontinuation are further discussed in final CSR.

***Assessor's comment*:**

Of the 179 subjects, 146 (81.6%) started the optional extension phase, with 77 subjects out of the 110 in the granule group continuing into the extension phase. Of those 146 subjects, 88 subjects (60.3%) completed the extension phase and 58 subjects (39.7%) discontinued treatment. The primary reasons for treatment discontinuation were withdrawal by parent/guardian (11.6%), physician decision (9.6%) and adverse event (8.2%). Adverse events leading to study treatment discontinuation will be further discussed when discussing safety results.

Protocol deviations

The most frequently reported PDs were other deviations (86.6%), treatment deviation (30.7%) and COVID-related deviations (26.3%). Among other deviations, the more frequent PDs were ocular exam not performed prior to starting study drug and/or at any scheduled visits (132 subjects; 73.7%), audiometry exam not performed prior to starting study drug and/or at any other scheduled visit (55 subjects; 30.7%), Echocardiogram not performed at Screening and/or EOT visit (43 subjects; 24.0%) and ECG not performed at Screening or, EOT visit (38 subjects; 21.2%).

COVID-related deviations were reported in 47 subjects (26.3%) of which the more commonly reported PDs were missed safety/efficacy assessments or study visit during extension phase due to COVID-19 (41 subjects; 22.9%), assessment/procedure changed during extension phase due to COVID-19 (22 subjects; 12.3%) and drug supply method changed during extension phase due to COVID-19 (21 subjects; 11.7%). COVID had minimal impact on the study.

For the ocular examinations, if at least one of assessments (visual acuity, tonometry, slit lamp examination, fundus oculi examination) was missed by a subject, it was considered as a PD. Ocular examinations have further been detailed in final CSR, Section 12.6.2.

***Assessor's comment*:**

No imbalance was observed between treatment arms as of 18 January 2021. Of the 179 subjects who received at least 1 dose of DFX granule formulation, 167 subjects (93.3%) had at least one protocol deviation (PD); 88.4% of subjects in the cross-over group and 96.4% in the granules group.

No overview of PDs has been provided; reported PDs are listed by study participant depending on the initial treatment allocation (DFX granule vs. DFX cross-over). Although no comparability between both groups is sought, PDs should have been provided in a tabular view listing at least the total PDs reported in each treatment group, PDs related to eligibility criteria and PDs regarding key procedures not performed as per protocol in order to appreciate the potential impact on data interpretability. A discussion of reported PDs by ICT status would have also been appreciated. However, this will not be further pursued as this assessment is focused on longer-term safety data for the granule formulation.

Treatment compliance

Compliance was assessed by the Investigator and/or study personnel every 4 weeks and information provided by the subject and/or caregiver was captured as described in Appendix 16.1.1-Protocol-Section 6.5.3.

The average dose, cumulative dose and percentage of planned dose taken were analyzed for subjects with complete start and end dates for all the records of the treatment with the granule formulation. For a total of 138 subjects (61 subjects in the cross-over group and 77 in the granule group) this analysis could be performed. The mean average planned dose of granules in the granules group was 19.41 mg/kg/day and the mean average actual dose received was 19.16 mg/kg/day. The mean (SD) percentage of planned granules dose taken was 92.92% (SD: 8.531) in the granules group. The mean average planned dose of granules for the cross-over group was 21.22 mg/kg/day and the mean average actual dose of granules received was 20.92 mg/kg/day. The mean (SD) percentage of planned granules dose taken was 93.32% (SD: 8.883) in the cross-over group.

***Assessor's comment*:**

The mean percentage of planned granules dose taken was similar between granules and crossover groups; 92.92% ±8.531 and 93.32% ± 8.883 %, indicating good compliance in both treatment groups.

Dose modifications

Dose change: In the granules group during the core or extension phase, dose change was reported in 94.5% of subjects. The reasons for at least one dose change were attributed to: as per protocol (92.7%), adverse event (66.4%), dosing error (55.5%), scheduling conflict (6.4%) and dispensing error (1.8%).

In the cross-over group during the extension phase, dose change was reported in 98.6% of subjects. The reasons for at least one dose change were attributed to: as per protocol (97.1%), adverse event (66.7%), dosing error (53.6%) and scheduling conflict (10.1%).

Dose interruption: In the granules group during the core or extension phase, dose interruption was reported in 80.0% of subjects. The reasons for at least one dose interruption was attributed to: as per protocol (11.8%), adverse event (61.8%), dosing error (44.5%) and scheduling conflict (5.5%).

In the cross-over group during the extension phase, dose interruption was reported in 85.5% of subjects. The reasons for at least one dose interruption were attributed to: as per protocol (15.9%), adverse event (50.7%), dosing error (53.6%) and scheduling conflict (10.1%).

A detailed description of AEs which required dose changes or interruptions are provided in final CSR, Section 12.2.4.

***Assessor's comment*:**

Dose change and/or dose interruptions were reported by 94.5% of subjects in the granules group and 98.6% of subjects in the cross-over group. In the granules group, reasons for dose changes were mosty as per protocol (92.7%), following the occurrence of an AD (66.4%) or due to a dosing error (55.5%). A similar trend was observed in the crossover group: 97.1% as per protocol, 66.7% following an adverse events and 53.6%

In both groups, reasons for dose interruptions were led by the occurrence of an AE (61.8% in the granules group vs. 50.7% in the crossover group) or by dosing error (44.5% vs. 53.6%), following by and per protocol dose interruptions (11.8% vs. 15.9%).

This high frequency of dose changes or interruptions due to dosing errors in both groups should be further discussed by the MAH. A detailed analysis of the potential impact of these frequent dosing errors on the efficacy and safety outcomes of study participants is also expected (**OC**).

As stated above, dose changes/interruptions due to an AE will be discussed further below, as part of the analysis of safety results.

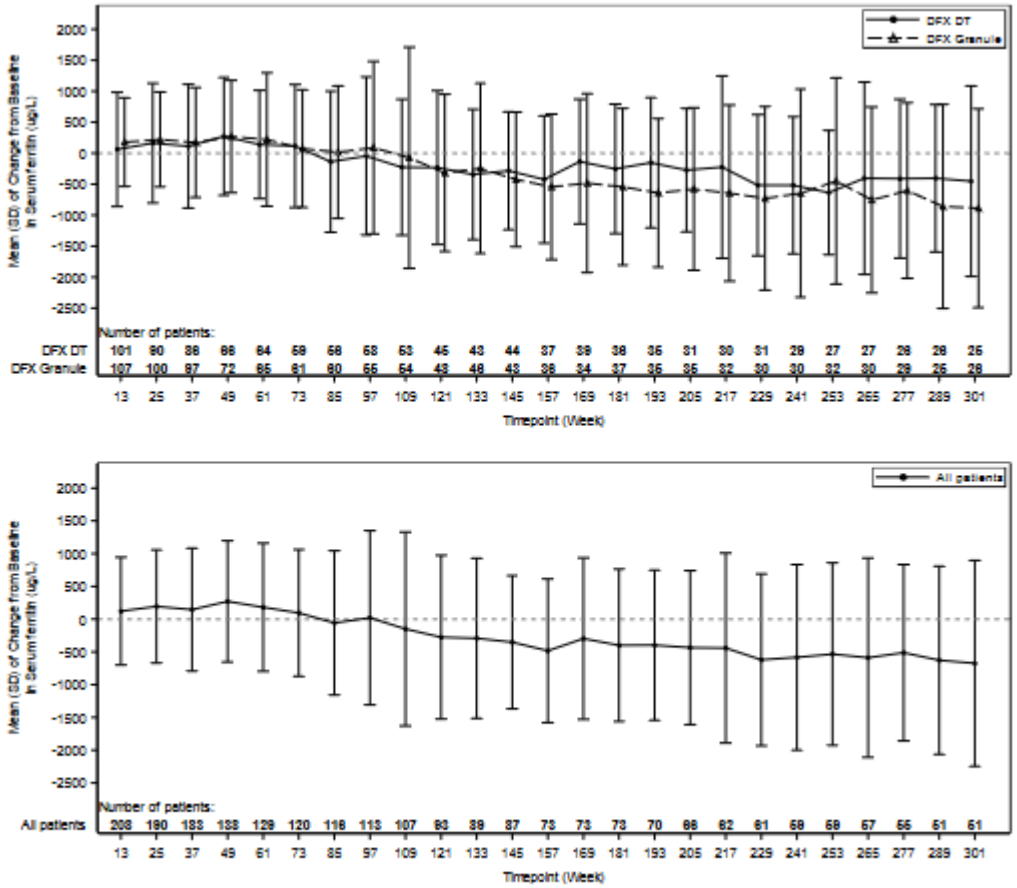
Changes from baseline in serum ferritin for the entire study

At baseline, the mean SF values in FAS-3 (224 subjects randomized with 112 subjects each in the DT and granules group) was 2274.0 µg/L in the DT group and 2293.7 µg/L in the granules group indicating that these subjects had moderate iron overload and were not different in both treatment groups for FAS-3.

A consistent decrease from baseline in mean SF was observed from Week 77 (-37.8 µg/L) onwards in the DT group (Week 105 (-219.6 µg/L), Week 157 (-424.3 µg/L), Week 209 (-193.3 µg/L), Week 261 (-395.2 µg/L), Week 305 (-525.2 µg/L). Similarly, a consistent decrease- from baseline in mean SF was observed from Week 105 (-228.7 µg/L) onwards in the granules group (Week 109 (-74.0 µg/L), Week 157 (-543.3 µg/L), Week 209 (-669.8 µg/L), Week 261 (-602.2 µg/L), Week 305 (-700.8 µg/L). However, due to a small number of subjects at the later time points, these results should be interpreted with caution.

The graphical representation of change in mean SF values for both the treatment groups by time-point based on FAS-3 is presented in the figure below.

Figure 2. Absolute change from baseline in Serum ferritin (ug/L) mean (SD) by timepoint and treatment during the entire study period (FAS-3)



Baseline is defined as the last non-missing value prior or on the day of randomization in DFX DT/granule group
Source: Figure 14.3-11.5a.

Serum ferritin results over the entire granule period

Note: Baseline in the granules group was defined as the initial Baseline value at study start (randomization) for subjects in granules group continuing in extension phase. Baseline-extension in the cross-over group was the date of the last assessment prior or equal to the start date of granules in the

extension phase as the pre-granule value that was the reference value for changes in the extension period.

In the granules group, the median SF values observed were 2030.0 µg/L at Baseline, 2310.0 µg/L at Week 53, 2026.5 µg/L at Week 105, 1224.5 µg/L at Week 157, 1497.0 µg/L at Week 209, 1447.5 µg/L at Week 261 and 1451.0 µg/L at Week 305 visit.

In the cross-over group, the median SF values observed were 2315.0 µg/L at Baseline-extension, 2376.0 µg/L at Week 53, 1776.0 µg/L at Week 105, 1529.0 µg/L at Week 157, 1448.0 µg/L at Week 209, 1227.0 µg/L at Week 261 and 1274.0 µg/L at Week 305 visit. Of note, for the cross-over group, the follow-up duration starts from Week 48 (end of core phase). Serum ferritin values for individual subjects during the study have been listed in CSR.

***Assessor's comment*:**

During the core period, mean baseline SF values were comparable between both treatments arms, indicating moderate iron overload. After 24 weeks of treatment, an overall decrease in serum ferritin (SF) was observed, with no statistically significant difference between the two treatment arms, suggesting there is no loss of efficacy associated with DFX granules compared with dispersible tablets.

For data collected throughout the entire granule period, the baseline for the crossover group was the last assessment prior or equal to the start date of granules in the extension phase. For safety set-4, the MAH chose to present median SF values rather than mean SF values, which did not allow to make meaningful comparisons. Detailed results provided in the final CSR confirmed the previously observed overall decrease in SF in both groups. These results are consistent with previous assessment and further support the interest of the granules formulations for patients with swallowing difficulties.

Safety results

Exposure

Table 9. Duration of exposure to study drug during the entire granule period (Safety Set-4)

Duration of exposure	DFX Cross-over N=69	DFX Granule N=110	All patients N=179
Exposure categories (months)-n (%)			
<6	7 (10.1)	7 (6.4)	14 (7.8)
6-<12	5 (7.2)	30 (27.3)	35 (19.6)
12-<24	14 (20.3)	15 (13.6)	29 (16.2)
24-<36	10 (14.5)	20 (18.2)	30 (16.8)
36-<48	4 (5.8)	4 (3.6)	8 (4.5)
48-<60	18 (26.1)	1 (0.9)	19 (10.6)
60-<72	11 (15.9)	31 (28.2)	42 (23.5)
72-<84	0	2 (1.8)	2 (1.1)

Exposure (months)			
n	69	110	179
Mean	36.3	34.1	34.9
SD	22.00	25.79	24.36
Median	35.1	25.9	28.6
Minimum	1.0	0.3	0.3
Maximum	61.0	72.1	72.1
Total patient years			
n	69	110	179
Mean	3.02	2.84	2.91
SD	1.833	2.150	2.030
Median	2.92	2.16	2.38
Minimum	0.1	0.0	0.0
Maximum	5.1	6.0	6.0

A patient is counted in only one duration range, per treatment.
Exposure (months): [(date of last study treatment) – (date of first study treatment) + 1]/30.4375.
Total patient-years: Overall duration of exposure (days) /365.25
Source: Table 14.3-1.4

In Safety set-4 (all subjects who received at least 1 dose of granule formulation during the core or extension phase, N=179; 69 in the cross-over and 110 in the granules group), the treatment exposure to granules for subjects initially randomized to the granules group in the core and who continued into the extension phase (N=110), as expected from the study design, had subjects with longer exposure; 30.0% of the subjects had exposure of > 60 months. The median duration of exposure in granules group was 25.9 months (range: 0.3-72.1).

As shown above, the median duration of exposure in the cross-over group in the extension phase was 35.1 months (range: 1.0-61.0). Treatment exposure to granules of >60 months was reported in 15.9% of subjects.

Assessor's comment:

The mean exposure during the entire granule period was higher in the granules group compared with the crossover group: 25.79 months vs. 22.00, with a third of subjects initially allocated to granules treated for more than 60 months.

Overview of adverse events (AEs)

Safety Set-4 included all subjects who received at least 1 dose of granule formulation during the core or extension phase. For subjects in granules group, AEs were reported since the initial randomization after the start of treatment in the core phase and continuing in the extension phase. For subjects in the cross-over group, AEs were reported for subjects since they crossed-over from DT to granules in the extension phase only.

Although the table format presented in the subsequent sections below is with both groups side by side, the treatment groups cannot be compared and need to be interpreted based on the different treatment periods they represent.

A brief overview of the different AE categories for the granules group in the core or extension phase and for the cross-over group in extension phase is presented in the table below; these are discussed in detail in the subsequent sections.

Table 10. Overall summary of adverse events by treatment during the entire granule period (Safety Set-4)

	DFX Cross-over N = 69		DFX Granule N = 110		All patients N = 179	
Category	All AEs n (%)	Severe AEs n (%)	All AEs n (%)	Severe AEs n (%)	All AEs n (%)	Severe AEs n (%)
Adverse events	64 (92.8)	19 (27.5)	106 (96.4)	45 (40.9)	170 (95.0)	64 (35.8)
Suspected	48 (69.6)	8 (11.6)	73 (66.4)	22 (20.0)	121 (67.6)	30 (16.8)
Serious adverse events	22 (31.9)	12 (17.4)	38 (34.5)	24 (21.8)	60 (33.5)	36 (20.1)
Suspected	4 (5.8)	2 (2.9)	7 (6.4)	5 (4.5)	11 (6.1)	7 (3.9)
AEs leading to study drug discontinuation	4 (5.8)	3 (4.3)	14 (12.7)	6 (5.5)	18 (10.1)	9 (5.0)
AEs requiring dose adjustment or/and interruption	42 (60.9)	9 (13.0)	70 (63.6)	23 (20.9)	112 (62.6)	32 (17.9)
AEs requiring additional therapy	56 (81.2)	13 (18.8)	96 (87.3)	28 (25.5)	152 (84.9)	41 (22.9)
Adverse events of special interest	52 (75.4)	10 (14.5)	79 (71.8)	27 (24.5)	131 (73.2)	37 (20.7)
All deaths	1 (1.4)		0		1 (0.6)	
On-treatment deaths	1 (1.4)		0		1 (0.6)	

Categories are not mutually exclusive. Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

In the granules group, AEs are reported since the initial randomization to the granules group in the core phase and continuing in the extension phase. In the cross-over group, AEs are reported for subjects since the subjects crossed-over from DT to granules in the extension phase only.

Both treatment groups are not comparable as the duration and the number of subjects between the two groups are not balanced.

On-treatment deaths: Deaths up to 30 days after the last study treatment are included.

Source: Tables 14.3.1-1.4

The overall summary of AEs during the extension phase only for subjects who continued into extension phase is presented in the table below.

Table 11. Overall summary of adverse events by treatment during the extension period for subjects who continued into extension phase (Safety Set 4)

	DFX Cross-over N = 69		DFX Granule N = 77		All patients N = 146	
Category	All AEs n (%)	Severe AEs n (%)	All AEs n (%)	Severe AEs n (%)	All AEs n (%)	Severe AEs n (%)
Adverse events	64 (92.8)	19 (27.5)	69 (89.6)	19 (24.7)	133 (91.1)	38 (26.0)
Suspected	48 (69.6)	8 (11.6)	45 (58.4)	10 (13.0)	93 (63.7)	18 (12.3)
Serious adverse events	22 (31.9)	12 (17.4)	20 (26.0)	11 (14.3)	42 (28.8)	23 (15.8)
Suspected	4 (5.8)	2 (2.9)	4 (5.2)	2 (2.6)	8 (5.5)	4 (2.7)
AEs leading to study drug discontinuation	4 (5.8)	3 (4.3)	9 (11.7)	3 (3.9)	13 (8.9)	6 (4.1)
AEs requiring dose adjustment or/and interruption	42 (60.9)	9 (13.0)	43 (55.8)	13 (16.9)	85 (58.2)	22 (15.1)
AEs requiring additional therapy	56 (81.2)	13 (18.8)	54 (70.1)	11 (14.3)	110 (75.3)	24 (16.4)

Adverse events of special interest	52 (75.4)	10 (14.5)	51 (66.2)	12 (15.6)	103 (70.5)	22 (15.1)
All deaths	1 (1.4)		0		1 (0.7)	
On-treatment deaths	1 (1.4)		0		1 (0.7)	

Categories are not mutually exclusive. Subjects with multiple events in the same category are counted only once in that category.

Subjects 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.

Source: Tables 14.3.1-1.4a

***Assessor's comment*:**

During the entire granule period, 170 out of 179 subjects (95.0%) had at least an AE. A third of subjects presented with at least a SAE, rarely suspected to be associated to treatment (6.1%). The proportion of subjects with AEs (regardless of type, severity or consequence) was overall comparable between the two groups. AEs leading to study drug discontinuation occurred in 18 subjects (10.1%) and AEs requiring dose adjustment or interruption concerned two thirds of subjects (62.6%). One subject in the crossover arm died during treatment.

A similar trend was observed for the 146 patients included in the extension period: 133 patients had at least an AE (91.1%), with almost a third of patients had at least one SAE, again rarely suspected to be associated to treatment (5.5%). Again, the proportion of subjects with SAEs was comparable between the two groups, probably considering a similar exposure to DFX treatment, regardless of the formulation (only granules or DTs then granules).

Adverse events by preferred term (PT)

Table 12. Adverse events (overall and severe AEs), regardless of study drug relationship by PT and treatment during the entire granule period (at least 5 percent in any treatment) (Safety Set-4)

	DFX Cross-over N=69		DFX Granule N=110		All Patients N=179	
Preferred term	**All AEs n (%)**	**Severe AEs n (%)**	**All AEs n (%)**	**Severe AEs n (%)**	**All AEs n (%)**	**Severe AEs n (%)**
-Any preferred term						
-Total	64 (92.8)	19 (27.5)	106 (96.4)	45 (40.9)	170 (95.0)	64 (35.8)
Upper respiratory tract infection	24 (34.8)	0	46 (41.8)	0	70 (39.1)	0

Pyrexia	15 (21.7)	0	39 (35.5)	4 (3.6)	54 (30.2)	4 (2.2)
Urine protein/creatinine ratio increased	36 (52.2)	2 (2.9)	39 (35.5)	7 (6.4)	75 (41.9)	9 (5.0)
Alanine aminotransferase increased	11 (15.9)	3 (4.3)	26 (23.6)	9 (8.2)	37 (20.7)	12 (6.7)
Cough	14 (20.3)	0	21 (19.1)	0	35 (19.6)	0
Pharyngitis	14 (20.3)	0	19 (17.3)	2 (1.8)	33 (18.4)	2 (1.1)
Aspartate aminotransferase increased	8 (11.6)	2 (2.9)	17 (15.5)	4 (3.6)	25 (14.0)	6 (3.4)
Nasopharyngitis	14 (20.3)	0	17 (15.5)	0	31 (17.3)	0
Diarrhoea	7 (10.1)	0	16 (14.5)	1 (0.9)	23 (12.8)	1 (0.6)
Transaminases increased	2 (2.9)	0	16 (14.5)	6 (5.5)	18 (10.1)	6 (3.4)
Gastroenteritis	8 (11.6)	2 (2.9)	15 (13.6)	3 (2.7)	23 (12.8)	5 (2.8)
Bilirubin conjugated increased	2 (2.9)	0	13 (11.8)	0	15 (8.4)	0
Vomiting	9 (13.0)	1 (1.4)	13 (11.8)	0	22 (12.3)	1 (0.6)
Abdominal pain	4 (5.8)	0	12 (10.9)	0	16 (8.9)	0
Influenza	3 (4.3)	1 (1.4)	12 (10.9)	0	15 (8.4)	1 (0.6)
Proteinuria	4 (5.8)	1 (1.4)	12 (10.9)	2 (1.8)	16 (8.9)	3 (1.7)
Rhinorrhoea	4 (5.8)	0	12 (10.9)	0	16 (8.9)	0
Headache	5 (7.2)	0	11 (10.0)	0	16 (8.9)	0
Oropharyngeal pain	3 (4.3)	0	10 (9.1)	0	13 (7.3)	0
Rash	2 (2.9)	0	10 (9.1)	0	12 (6.7)	0
COVID-19	9 (13.0)	0	9 (8.2)	1 (0.9)	18 (10.1)	1 (0.6)
Rhinitis	3 (4.3)	0	9 (8.2)	0	12 (6.7)	0
Rhinitis allergic	3 (4.3)	0	9 (8.2)	0	12 (6.7)	0
Urinary tract infection	6 (8.7)	1 (1.4)	9 (8.2)	0	15 (8.4)	1 (0.6)
Abdominal pain upper	3 (4.3)	0	8 (7.3)	0	11 (6.1)	0
Blood bilirubin increased	4 (5.8)	0	8 (7.3)	1 (0.9)	12 (6.7)	1 (0.6)
Tonsillitis	6 (8.7)	1 (1.4)	8 (7.3)	1 (0.9)	14 (7.8)	2 (1.1)
Blood creatinine increased	3 (4.3)	0	7 (6.4)	1 (0.9)	10 (5.6)	1 (0.6)
Bronchitis	4 (5.8)	0	7 (6.4)	0	11 (6.1)	0
Arthralgia	0	0	6 (5.5)	0	6 (3.4)	0
Dental caries	3 (4.3)	0	6 (5.5)	0	9 (5.0)	0
Gastritis	4 (5.8)	0	6 (5.5)	0	10 (5.6)	0
Otitis media	1 (1.4)	0	6 (5.5)	0	7 (3.9)	0
Viral infection	4 (5.8)	0	6 (5.5)	0	10 (5.6)	0
Epistaxis	4 (5.8)	0	3 (2.7)	0	7 (3.9)	0
Constipation	4 (5.8)	0	2 (1.8)	0	6 (3.4)	0
Sinusitis	4 (5.8)	1 (1.4)	0	0	4 (2.2)	1 (0.6)

Preferred terms are sorted in descending frequency of all AEs column, as reported in the DFX Granules treatment group.

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

A patient with multiple adverse events across preferred terms is counted only once in the total row.

MedDRA Version 26.1 has been used for the reporting of adverse events.

Both treatment groups are not comparable as the duration and the number of subjects between the two groups are not balanced.

Source: Table 14.3.1-1.8

As shown in the table above, the most commonly (≥ 20%) reported AEs (by PT) in the granules group during the core or extension phase were: upper respiratory tract infection (41.8%), pyrexia (35.5%), urine protein/creatinine ratio increased (35.5%) and alanine aminotransferase increased (23.6%).

The most commonly (≥ 20%) reported AEs (by PT) in the cross-over group during the extension phase were: urine protein/creatinine ratio increased (52.2%), upper respiratory tract infection (34.8%), pyrexia (21.7%), cough (20.3%), nasopharyngitis (20.3%) and pharyngitis (20.3%).

Adverse events (overall and severe AEs), regardless of study drug relationship by SOC, PT and treatment during the extension period only is presented in final CSR.

***Assessor's comment*:**

During the core phase (data cut-off: 18 January 2021), the most commonly reported AEs (incidence ≥ 20% in either group) by PT (DT group vs. granules group) were upper respiratory tract infection (29.7% vs. 28.2%), pyrexia (23.4% vs. 26.4%), and urine protein/creatinine ratio increased (34.2% vs 24.5%).

During the entire granules period (data cut-off; 26 January 2024), reported AEs by PT in the granules group were led upper respiratory tract infection (41.8%), pyrexia and urine protein/creatinine ratio increased (35.5%) and alanine aminotransferase increased (23.6%). In the crossover group, urine protein/creatinine ratio increased (52.2%), upper tract infection (34.8%), pyrexia (21.7%), cough, pharyngitis and nasopharyngitis (20.3% each) were the most common AEs reported by PT. Events were rarely severe (≥10%), which is overall consistent with safety data at the end of the core phase.

Adverse events leading to dose modifications or requiring additional therapy

- Adverse events leading to discontinuation

Table 13. Adverse events leading to study drug discontinuation (overall and severe AEs), regardless of study drug relationship by preferred term and treatment during the entire granule period (Safety Set-4)

	DFX Cross-over N=69		DFX Granule N=110		All Patients N=179	
Preferred term	All AEs n (%)	Severe AEs n (%)	All AEs n (%)	Severe AEs n (%)	All AEs n (%)	Severe AEs n (%)
-Any preferred term						
-Total	4 (5.8)	3 (4.3)	14 (12.7)	6 (5.5)	18 (10.1)	9 (5.0)
Alanine aminotransferase increased	0	0	3 (2.7)	0	3 (1.7)	0
Blood bilirubin increased	0	0	2 (1.8)	0	2 (1.1)	0
Transaminases increased	0	0	2 (1.8)	2 (1.8)	2 (1.1)	2 (1.1)
Abdominal pain upper	0	0	1 (0.9)	0	1 (0.6)	0
Aspartate aminotransferase increased	0	0	1 (0.9)	0	1 (0.6)	0
Drug reaction with eosinophilia and systemic symptoms	0	0	1 (0.9)	1 (0.9)	1 (0.6)	1 (0.6)
Headache	0	0	1 (0.9)	0	1 (0.6)	0
Hepatitis acute	0	0	1 (0.9)	1 (0.9)	1 (0.6)	1 (0.6)
Jaundice cholestatic	0	0	1 (0.9)	1 (0.9)	1 (0.6)	1 (0.6)
Overdose	0	0	1 (0.9)	0	1 (0.6)	0
Retinal pigmentation	0	0	1 (0.9)	0	1 (0.6)	0
Upper gastrointestinal haemorrhage	0	0	1 (0.9)	1 (0.9)	1 (0.6)	1 (0.6)

Urine protein/creatinine ratio increased	0	0	1 (0.9)	0	1 (0.6)	0
Drug-induced liver injury	1 (1.4)	0	0	0	1 (0.6)	0
Fanconi syndrome acquired	3 (4.3)	2 (2.9)	0	0	3 (1.7)	2 (1.1)
Sudden death	1 (1.4)	1 (1.4)	0	0	1 (0.6)	1 (0.6)

Preferred terms are sorted in descending frequency of all AEs column, as reported in the DFX Granules treatment group.

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

A patient with multiple adverse events across preferred terms is counted only once in the total row.

MedDRA Version 26.1 has been used for the reporting of adverse events.

Source: Table 14.3.1-6.4

In the granules group during the core or extension phase, AEs leading to study drug discontinuation were reported in 12.7% of subjects. AEs leading to study drug discontinuation reported in >1 subject each were ALT increased (2.7%), blood bilirubin increased, and transaminases increased (1.8% each). From the previous data cut-off date (18-Jan-2021), 1 additional AE of blood bilirubin increased lead to study drug discontinuation in the granules group.

In the cross-over group during the extension phase, AEs leading to study drug discontinuation were reported in 5.8% of subjects. AEs leading to study drug discontinuation reported were drug-induced liver injury and sudden death (1.4% each) and Fanconi syndrome acquired (4.3%). From the previous data cut-off date (18-Jan-2021), 1 additional event leading to treatment discontinuation was reported (sudden death) in the cross-over group.

***Assessor's comment*:**

During the entire granule period, 18 subjects had at least 1 AE leading to treatment discontinuation, 9 of them with severe AEs. In the granules group, 14 patients experienced an AE leading to treatment discontinuation, mainly under the SOC 'Investigations': ALT increase (3 patients, 2.7%), blood bilirubin increase (2 subjects, 1.8%), severe transaminases increase (2 subjects, 1.8%).

Among the other AEs reported, the following were classified as severe: drug reaction with eosinophilia and systemic symptoms, hepatitis acute, jaundice cholestatic and upper gastrointestinal haemorrhage (1 subject each, 0.9%).

In the crossover group, 4 subjects (5.8%) presented an AE leading to treatment discontinuation; acquired Fanconi syndrome (3 subjects, 4.3%). Drug-induced liver injury and sudden death (1 subject each, 1.4%). Only one case of acquired Fanconi syndrome was classified as severe.

Of all the reported AEs that resulted in discontinuation of treatment for entire granule period, only two events occurred after the previous cut-off of 18 January 2021, a non-severe AE of blood bilirubin increased in the granule group and the sudden death reported in the crossover arm, which will be discussed in the dedicated section below.

- Adverse events leading to dose adjustment and/or interruption

In the granules group during the core or extension phase, 63.6% of subjects had AEs that required dose adjustments/interruptions. The most commonly (≥ 10%) reported AEs that required dose adjustments/interruptions were: urine protein/creatinine ratio increased (23.6%), ALT increased (13.6%), AST increased (10.9%) and bilirubin conjugated increased (10.0%).

In the cross-over group during the extension phase, 60.9% of subjects had AEs that required dose adjustments/interruptions. The most commonly (≥ 10%) reported AEs that required dose

adjustments/interruptions were urine protein/creatinine ratio increased (33.3%). All other AEs that required dose adjustments/interruptions were reported in <10% of subjects.

- Adverse events requiring additional therapy

In the granules group during the core or extension phase, 87.3% of subjects had AEs that required additional therapy. The AEs requiring additional therapy noted in ≥ 10% of the subjects in the granules group were: upper respiratory tract infection (31.8%), pyrexia (30.9%), pharyngitis (16.4%), cough (14.5%), nasopharyngitis (11.8%), gastroenteritis and influenza (10.0% each).

In the cross-over group during the extension phase, 81.2% of subjects had AEs that required additional therapy. The AEs requiring additional therapy noted in > 10% of the subjects in the cross-over group were: upper respiratory tract infection (27.5%), pharyngitis (20.3%), pyrexia (15.9%), nasopharyngitis (14.5%), cough (13.0%), gastroenteritis and COVID-19 (10.1% each).

Assessor's comment:

For the entire granule period, adverse events leading to a dose interruption were not distinguished from those leading to a dose adjustment (presumably dose reduction), which makes it impossible to compare with the corresponding AEs reported at the last cut-off. The MAH is therefore requested to provide a comprehensive analysis distinguishing AEs leading to a dose interruption from those leading to a dose adjustment (please specify: dose reduction / increase) during the core period compared with those reported during the extension period. A comprehensive discussion of the long-term safety profile of the granule form in the light of these results is expected (**OC**).

Most AEs requiring additional therapy were related to infections/inflammations (upper respiratory tract infection, nasopharyngitis, gastroenteritis, influenza and COVID-19 infections) and corresponding symptomatic manifestations (pyrexia, cough), which is consistent with protocol recommendations and current clinical practice.

Suspected drug-related AEs

Table 14. Adverse events (overall and severe AEs), suspected to be study drug-related in greater than 1 percent in all subjects (severe AEs in both groups included) by preferred term and treatment during the entire granule period (Safety Set-4)

	DFX Cross-over N=69		DFX Granule N=110		All Patients N=179	
Preferred term	All AEs n (%)	Severe AEs n (%)	All AEs n (%)	Severe AEs n (%)	All AEs n (%)	Severe AEs n (%)
-Any preferred term						
Total	48 (69.6)	8 (11.6)	73 (66.4)	22 (20.0)	121 (67.6)	30 (16.8)
Urine protein/creatinine ratio increased	33 (47.8)	2 (2.9)	33 (30.0)	6 (5.5)	66 (36.9)	8 (4.5)
Alanine aminotransferase increased	9 (13.0)	3 (4.3)	17 (15.5)	7 (6.4)	26 (14.5)	10 (5.6)
Transaminases increased	1 (1.4)	0	13 (11.8)	6 (5.5)	14 (7.8)	6 (3.4)
Proteinuria	4 (5.8)	1 (1.4)	12 (10.9)	2 (1.8)	16 (8.9)	3 (1.7)
Aspartate aminotransferase increased	5 (7.2)	2 (2.9)	10 (9.1)	4 (3.6)	15 (8.4)	6 (3.4)
Bilirubin conjugated increased	2 (2.9)	0	7 (6.4)	0	9 (5.0)	0
Blood creatinine increased	2 (2.9)	0	6 (5.5)	1 (0.9)	8 (4.5)	1 (0.6)
Blood bilirubin increased	1 (1.4)	0	4 (3.6)	0	5 (2.8)	0

Abdominal pain	2 (2.9)	0	3 (2.7)	0	5 (2.8)	0
Diarrhoea	3 (4.3)	0	3 (2.7)	0	6 (3.4)	0
Haematuria	0	0	3 (2.7)	0	3 (1.7)	0
Vomiting	3 (4.3)	0	3 (2.7)	0	6 (3.4)	0
Abdominal pain upper	0	0	2 (1.8)	0	2 (1.1)	0
Nausea	2 (2.9)	0	2 (1.8)	0	4 (2.2)	0
Rash	0	0	2 (1.8)	0	2 (1.1)	0
Accidental overdose	1 (1.4)	0	1 (0.9)	0	2 (1.1)	0
Blood bicarbonate decreased	1 (1.4)	0	1 (0.9)	0	2 (1.1)	0
Conductive deafness	2 (2.9)	0	1 (0.9)	0	3 (1.7)	0
Creatinine renal clearance decreased	1 (1.4)	0	1 (0.9)	0	2 (1.1)	0
Drug reaction with eosinophilia and systemic symptoms	0	0	1 (0.9)	1 (0.9)	1 (0.6)	1 (0.6)
Hepatitis acute	0	0	1 (0.9)	1 (0.9)	1 (0.6)	1 (0.6)
Jaundice cholestatic	0	0	1 (0.9)	1 (0.9)	1 (0.6)	1 (0.6)
Pancreatitis acute	0	0	1 (0.9)	1 (0.9)	1 (0.6)	1 (0.6)
Upper gastrointestinal haemorrhage	0	0	1 (0.9)	1 (0.9)	1 (0.6)	1 (0.6)
Deafness neurosensory	2 (2.9)	0	0	0	2 (1.1)	0
Fanconi syndrome acquired	3 (4.3)	2 (2.9)	0	0	3 (1.7)	2 (1.1)
Serum ferritin decreased	2 (2.9)	0	0	0	2 (1.1)	0

Preferred terms are sorted in descending frequency of all AEs column, as reported in the DFX Granules treatment group.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple adverse events across preferred terms is counted only once in the total row.
MedDRA Version 26.1 has been used for the reporting of adverse events.
Both treatment groups are not comparable as the duration and the number of subjects between the two groups are not balanced.
Source: Table 14.3.1-3.4

In the granules group during the core or extension phase, 66.4% of subjects had AEs suspected to be study drug related. Most PTs were reported in <10% of the subjects with the exception of urine protein/creatinine ratio increased (30.0%), ALT increased (15.5%), transaminases increased (11.8%), and proteinuria (10.9%).

In the cross-over group during the extension phase, 69.6% of subjects had AEs suspected to be study-drug related. Most PTs were reported in <10% of the subjects with the exception of urine protein/creatinine ratio increased (47.8%) and ALT increased (13.0%).

In the granules group during the core or extension phase, overall 40.9% of subjects had severe AEs and 20.0% of subjects had severe AEs suspected to be study drug related by Investigator.

None of the severe AEs were reported in < 5% of subjects except for ALT increased (8.2%), urine protein/creatinine ratio increased (6.4%) and transaminases increased (5.5%).

In the cross-over group during the extension phase, 27.5% of subjects had severe AEs and 11.6% of subjects had severe AEs suspected to be study drug related by Investigator. None of the severe AEs were reported in < 5% of subjects.

***Assessor's comment*:**

During the entire granule period, 121 patients (67.6%) experienced at least a suspected drug-related AE: 73 subjects in the granules group (66.4%), including 22 subjects with at least severe AE and 48 subjects in the crossover group (69.6%), 8 of them (11.6%) with at least severe AE.

Suspected drug-related AEs in both groups were led by AEs under the SOC 'Investigations': urine protein/creatinine ratio increased (30% in the granules group and 47.8% in the crossover group), ALT increase (15.5% and 13.0%), transaminase increase (11.8% and 1.4%), proteinuria (10.9% and 5.8%) AST increase (9.1% and 7.2%). This is overall consistent with previous assessment for this study and the known safety profile of deferasirox granules.

Serious adverse events (SAEs) and deaths

Serious adverse events

	DFX Cross-over N=69		DFX Granule N=110		All Patients N=179	
Preferred term	All AEs n (%)	Severe AEs n (%)	All AEs n (%)	Severe AEs n (%)	All AEs n (%)	Severe AEs n (%)
-Any preferred term						
-Total	22 (31.9)	12 (17.4)	38 (34.5)	24 (21.8)	60 (33.5)	36 (20.1)
Gastroenteritis	4 (5.8)	2 (2.9)	5 (4.5)	3 (2.7)	9 (5.0)	5 (2.8)
Pyrexia	1 (1.4)	0	5 (4.5)	3 (2.7)	6 (3.4)	3 (1.7)
Sickle cell anaemia with crisis	0	0	5 (4.5)	3 (2.7)	5 (2.8)	3 (1.7)
Acute chest syndrome	1 (1.4)	0	3 (2.7)	1 (0.9)	4 (2.2)	1 (0.6)
Cholelithiasis	0	0	3 (2.7)	2 (1.8)	3 (1.7)	2 (1.1)
Bronchiolitis	0	0	2 (1.8)	1 (0.9)	2 (1.1)	1 (0.6)
Dehydration	2 (2.9)	2 (2.9)	2 (1.8)	1 (0.9)	4 (2.2)	3 (1.7)
Dengue fever	1 (1.4)	0	2 (1.8)	1 (0.9)	3 (1.7)	1 (0.6)
Hypokalaemia	0	0	2 (1.8)	2 (1.8)	2 (1.1)	2 (1.1)
Systemic viral infection	0	0	2 (1.8)	0	2 (1.1)	0
Upper gastrointestinal haemorrhage	0	0	2 (1.8)	2 (1.8)	2 (1.1)	2 (1.1)
Upper respiratory tract infection	2 (2.9)	0	2 (1.8)	0	4 (2.2)	0
Overdose	1 (1.4)	0	1 (0.9)	0	2 (1.1)	0
Pain in extremity	0	0	1 (0.9)	1 (0.9)	1 (0.6)	1 (0.6)
Pancreatitis acute	0	0	1 (0.9)	1 (0.9)	1 (0.6)	1 (0.6)
Pharyngitis	2 (2.9)	0	1 (0.9)	1 (0.9)	3 (1.7)	1 (0.6)
Pneumonia	1 (1.4)	1 (1.4)	1 (0.9)	0	2 (1.1)	1 (0.6)
Pneumonia bacterial	0	0	1 (0.9)	1 (0.9)	1 (0.6)	1 (0.6)
Pneumonia respiratory syncytial viral	0	0	1 (0.9)	1 (0.9)	1 (0.6)	1 (0.6)
Stress ulcer	0	0	1 (0.9)	1 (0.9)	1 (0.6)	1 (0.6)
Tension headache	0	0	1 (0.9)	1 (0.9)	1 (0.6)	1 (0.6)
Thrombocytopenia	0	0	1 (0.9)	1 (0.9)	1 (0.6)	1 (0.6)
Tonsillitis	2 (2.9)	1 (1.4)	1 (0.9)	1 (0.9)	3 (1.7)	2 (1.1)
Transfusion reaction	0	0	1 (0.9)	1 (0.9)	1 (0.6)	1 (0.6)

Viral upper respiratory tract infection	0	0	1 (0.9)	1 (0.9)	1 (0.6)	1 (0.6)
Bacterial infection	1 (1.4)	1 (1.4)	0	0	1 (0.6)	1 (0.6)
Dengue haemorrhagic fever	1 (1.4)	1 (1.4)	0	0	1 (0.6)	1 (0.6)
Diabetic ketoacidosis	1 (1.4)	1 (1.4)	0	0	1 (0.6)	1 (0.6)
Electrolyte imbalance	1 (1.4)	1 (1.4)	0	0	1 (0.6)	1 (0.6)
Fanconi syndrome acquired	3 (4.3)	2 (2.9)	0	0	3 (1.7)	2 (1.1)
Foot fracture	1 (1.4)	1 (1.4)	0	0	1 (0.6)	1 (0.6)
Gastrointestinal haemorrhage	1 (1.4)	1 (1.4)	0	0	1 (0.6)	1 (0.6)
Haemoglobin decreased	2 (2.9)	2 (2.9)	0	0	2 (1.1)	2 (1.1)
Influenza	1 (1.4)	1 (1.4)	0	0	1 (0.6)	1 (0.6)
Ligament sprain	1 (1.4)	1 (1.4)	0	0	1 (0.6)	1 (0.6)
Pleural effusion	1 (1.4)	1 (1.4)	0	0	1 (0.6)	1 (0.6)
Scarlet fever	1 (1.4)	1 (1.4)	0	0	1 (0.6)	1 (0.6)
Sinusitis	2 (2.9)	1 (1.4)	0	0	2 (1.1)	1 (0.6)
Sudden death	1 (1.4)	1 (1.4)	0	0	1 (0.6)	1 (0.6)
Urinary tract infection	1 (1.4)	1 (1.4)	0	0	1 (0.6)	1 (0.6)
Urticaria	1 (1.4)	1 (1.4)	0	0	1 (0.6)	1 (0.6)
Vomiting	1 (1.4)	1 (1.4)	0	0	1 (0.6)	1 (0.6)

Preferred terms are sorted in descending frequency of all AEs column, as reported in the DFX Granules treatment group.

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

A patient with multiple adverse events across preferred terms is counted only once in the total row.

MedDRA Version 26.1 has been used for the reporting of adverse events.

Source: Table 14.3.1-4.4

In the granules group during the core or extension phase, 34.5% of subjects reported SAEs (regardless of study drug relationship) and 21.8% of subjects reported severe SAEs. All SAEs were reported in either 1 or 2 subjects with the exception of gastroenteritis, pyrexia and sickle cell anaemia with crisis (4.5% each, severe in 2.7%), acute chest syndrome and cholelithiasis (2.7% each, severe in 0.9% and 1.8%, respectively).

In the cross-over group during the extension phase, 31.9% of subjects reported SAEs (regardless of study drug relationship) and 17.4% subjects reported severe SAEs. All SAEs were reported in either 1 or 2 subjects except for gastroenteritis (5.8%) and Fanconi syndrome acquired (4.3%). Severe SAEs were reported in either 1 or 2 subjects.

- Suspected drug-related SAEs

In the granules group during the core or extension phase, SAEs suspected to be study drug-related were low (6.4%): gastritis, pancreatitis acute, upper gastrointestinal hemorrhage, hepatitis acute, jaundice cholestatic, blood creatinine increased, urine protein/creatinine ratio increased and drug reaction with eosinophilia and systemic symptoms with 1 subject (0.9%) each. No new suspected SAEs were reported from the last data cut-off date (18-Jan-2021) in the granules group.

In the cross-over group during the extension phase, SAEs suspected to be study drug-related were low (5.8%): drug-induced liver injury and overdose (1 subject; 1.4% each) and Fanconi syndrome acquired (3 subjects; 4.3%). From the previous data cut-off date (18-Jan-2021), 1 additional suspected SAE of overdose was reported in the cross-over group.

***Assessor's comment*:**

Throughout the entire granule period, 60 subjects (33.5%) experienced at least one SAE, a fifth of which was severe (36 subjects, 20.1%).

In the granules group, 38 subjects had at least a SAE, 24 of them with a severe one. Most AEs were related to sickle cell anaemia with crisis (5 subjects, 4.5%), acute chest syndrome (3 subjects, 2.7%) and infections/inflammation or associated symptoms: gastroenteritis and pyrexia (5 subjects each, 4.5%), cholelithiasis (3 subjects, 2.7%), bronchiolitis, systemic viral infection and dengue fever (2 subjects each, 2.8%). Serious cases of dehydration, hypokalaemia, upper gastrointestinal haemorrhage were also reported in 2 subjects each.

In the crossover group, 12 subjects experienced at least one SAE, mostly related to infections/inflammations or associated symptoms. Three SAEs of Fanconi acquired syndrome (2 of them being severe) were also reported, as well as severe cases of dehydration and Hb decrease in two subjects each.

Overall, there were few suspected drug-related SAEs: 6.4% in the granules group and 5.8% in the crossover group. Only one suspected drug-related SAE (Fanconi syndrome acquired in the crossover group) occurred after the last cut-off date.

Deaths

One on-treatment (within 30 days of last treatment) death was reported in the cross-over group during the extension phase which was not suspected to be related to the study treatment. One subject (ICT pre-treated subject with Beta-thalassemia major) had sudden death. No autopsy was performed.

***Assessor's comment*:**

One on-treatment death occurred in the crossover group during the extension phase. According to the MAH, this death was not suspected to be drug-related. However, according to the narrative provided, the patient has never been treated at the adequate dose throughout their study participation. Possible impact of repeated dosing errors on their safety outcomes should be further discussed, based on a comprehensive description of the changes in their condition during treatment, as the diagrams provided in the narrative are not considered sufficiently precise to rule on this aspect (**OC**).

Adverse events of special interest (AESIs)

All AESI groupings are defined through the use of PT, High Level Terms (HLT), SOC, Standardized MedDRA Queries (SMQ), Novartis MedDRA Queries (NMQ) or through a combination of these components. The case retrieval sheet used for AESI is provided in final CSR, Listing 14.3.2-6.

A brief overview of the AESIs are presented in the table below; these are discussed in detail in the subsequent sections.

Table 15. Adverse events of special interest, regardless of study drug relationship by grouping, preferred term and treatment during the entire granule period (Safety Set-4)

Group term (Risk Name) Preferred term	DFX Cross-over N=69 n (%)	DFX Granule N=110 n (%)	All patients N=179 n (%)
-Any adverse event of special interest			
-Total	52 (75.4)	79 (71.8)	131 (73.2)
Gastrointestinal hemorrhages Ulcers Oesophagitis	3 (4.3)	4 (3.6)	7 (3.9)
Upper gastrointestinal haemorrhage	0	2 (1.8)	2 (1.1)
Anal haemorrhage	0	1 (0.9)	1 (0.6)
Haematemesis	0	1 (0.9)	1 (0.6)
Stress ulcer	0	1 (0.9)	1 (0.6)
Gastrointestinal haemorrhage	1 (1.4)	0	1 (0.6)
Haematochezia	1 (1.4)	0	1 (0.6)
Oesophagitis	1 (1.4)	0	1 (0.6)
Hearing loss	5 (7.2)	5 (4.5)	10 (5.6)
Deafness	1 (1.4)	2 (1.8)	3 (1.7)
Conductive deafness	2 (2.9)	1 (0.9)	3 (1.7)
Deafness bilateral	1 (1.4)	1 (0.9)	2 (1.1)
Deafness neurosensory	2 (2.9)	1 (0.9)	3 (1.7)
Deafness unilateral	0	1 (0.9)	1 (0.6)
Mixed deafness	0	1 (0.9)	1 (0.6)
Lens opacities Retinal changes and Optic neuritis	0	2 (1.8)	2 (1.1)
Lenticular pigmentation	0	1 (0.9)	1 (0.6)
Retinal pigmentation	0	1 (0.9)	1 (0.6)
Visual acuity reduced	0	1 (0.9)	1 (0.6)
Visual acuity tests abnormal	0	1 (0.9)	1 (0.6)
Liver disorders_Hepatic failure	1 (1.4)	0	1 (0.6)
Drug-induced liver injury	1 (1.4)	0	1 (0.6)
Liver disorders_Increased liver transaminases	16 (23.2)	46 (41.8)	62 (34.6)
Alanine aminotransferase increased	11 (15.9)	26 (23.6)	37 (20.7)
Aspartate aminotransferase increased	8 (11.6)	17 (15.5)	25 (14.0)
Transaminases increased	2 (2.9)	16 (14.5)	18 (10.1)
Bilirubin conjugated increased	2 (2.9)	13 (11.8)	15 (8.4)
Blood bilirubin increased	4 (5.8)	8 (7.3)	12 (6.7)
Hyperbilirubinaemia	0	2 (1.8)	2 (1.1)
Hepatic enzyme increased	0	1 (0.9)	1 (0.6)
Hepatitis	0	1 (0.9)	1 (0.6)
Hepatitis acute	0	1 (0.9)	1 (0.6)
Hepatomegaly	0	1 (0.9)	1 (0.6)
Liver function test abnormal	0	1 (0.9)	1 (0.6)
Liver function test increased	0	1 (0.9)	1 (0.6)
Gamma-glutamyltransferase increased	1 (1.4)	0	1 (0.6)
Peripheral blood cytopenias	5 (7.2)	7 (6.4)	12 (6.7)
Transfusion reaction	2 (2.9)	3 (2.7)	5 (2.8)
Autoimmune haemolytic anaemia	0	1 (0.9)	1 (0.6)
Febrile neutropenia	0	1 (0.9)	1 (0.6)
Neutropenia	0	1 (0.9)	1 (0.6)
Neutrophil count decreased	0	1 (0.9)	1 (0.6)
Thrombocytopenia	0	1 (0.9)	1 (0.6)

Alloimmunisation	1 (1.4)	0	1 (0.6)
Haemolytic anaemia	1 (1.4)	0	1 (0.6)
Leukopenia	1 (1.4)	0	1 (0.6)
Renal disorders_Acute renal failure	1 (1.4)	0	1 (0.6)
Nephropathy toxic	1 (1.4)	0	1 (0.6)
Renal disorders_Increased serum creatinine	4 (5.8)	8 (7.3)	12 (6.7)
Blood creatinine increased	3 (4.3)	7 (6.4)	10 (5.6)
Creatinine renal clearance decreased	1 (1.4)	1 (0.9)	2 (1.1)
Glomerular filtration rate decreased	0	1 (0.9)	1 (0.6)
Renal disorders_Proteinuria	40 (58.0)	49 (44.5)	89 (49.7)
Urine protein/creatinine ratio increased	36 (52.2)	39 (35.5)	75 (41.9)
Proteinuria	4 (5.8)	12 (10.9)	16 (8.9)
Urine protein/creatinine ratio abnormal	0	1 (0.9)	1 (0.6)
Renal disorders_Renal tubular disorders	4 (5.8)	0	4 (2.2)
Fanconi syndrome acquired	3 (4.3)	0	3 (1.7)
Nephropathy toxic	1 (1.4)	0	1 (0.6)
Severe Cutaneous adverse reactions	0	1 (0.9)	1 (0.6)
Drug reaction with eosinophilia and systemic symptoms	0	1 (0.9)	1 (0.6)

Grouped terms are presented alphabetically on each level; preferred terms are sorted within grouped terms in descending frequency of all AEs, as reported in the DFX Granules treatment group.

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

A patient with multiple adverse events within a grouped term is counted only once in the total row.

MedDRA Version 26.1 has been used for the reporting of adverse events.

Source: Table 14.3.1-10.10

Liver disorders

- Increased liver transaminases

In the granules group during the core or extension phase, 41.8% of subjects had liver-related AESIs, 32.7% of subjects had AEs suspected to be study drug-related by the Investigator. One SAE (acute Hepatitis) was reported in 1 subject (0.9%). Liver-related AESI requiring dose adjustments or interruptions were reported for 27.3% of subjects. Number of subjects who discontinued study treatment due to liver disorders (5.5%) or required additional therapy was low (6.4%).

In the cross-over group during the extension phase, 23.2% of subjects had liver-related AESI, 17.4% had AEs suspected to be study drug-related by the Investigators. One subject had an SAE of drug-induced liver injury which was managed by non-drug therapy and discontinued the study treatment. Liver-related AESI requiring dose adjustments or interruptions were reported in 10.1% of subjects. Number of subjects who discontinued study treatment due to liver disorders (1.4%) or required additional therapy was low (4.3%).

- Hepatic failure

None of the subjects in the granules group reported AESIs of hepatic failure during the core or extension phase.

In the cross-over group during the extension phase, 1 subject had a SAE of drug induced liver injury which was suspected to be study drug related. This event led to study discontinuation, required additional therapy and the subject recovered.

Details of increases in ALT and AST based on laboratory data are provided further below in the section dedicated to clinical chemistry abnormalities.

***Assessor's comment*:**

Consistently with the known safety profile of DFX, liver transaminases were common during the study.

During the entire granules period, around 40% of subjects in the granules group had increased liver transaminases, 75% of them being drug-related and about a third of them required a dose adjustment. Few subsequent treatment discontinuation or need for additional therapy were reported (5.5% and 6.4%, respectively).

A similar trend was observed in the crossover group during the extension phase with a lower incidence of events due to the shorter treatment period.

One case of hepatic failure was reported in the crossover group: one patient had a SAE of drung-induced liver injury which was suspected to be drug-related. The patient recovered after study discontinuation and additional therapy. Such cases have been reported in the post-marketing setting.

Renal disorders

- Proteinuria

In the granules group during the core or extension phase, AESI of proteinuria were reported in 44.5% of subjects, 40.0% of events were suspected to be study drug related and 1 subject had an SAE (urine protein/creatinine ratio increased). One subject discontinued the study, 32.7% of subjects required dose adjustments/ interruptions and none of the subjects required additional therapy.

In the cross-over group during the extension phase, 58.0% of subjects had AESI of proteinuria, 53.6% events were suspected to be study drug related and none of the subjects had SAEs). There were no discontinuations, 37.7% of subjects required dose adjustments/ interruption and none of the subjects required additional therapy.

- Increased serum creatinine

In granules group during the core or extension phase, 7.3% of subjects had AESI of increased serum creatinine and 6.4% of the AEs were suspected to be study drug related and 1 subject had an SAE (blood creatinine increased). The subjects requiring dose adjustment/interruption was 6.4% and 1 subject required additional therapy. None of the AEs led to discontinuations.

In the cross-over group during the extension phase, 5.8% of subjects had AESI of increased serum creatinine, 4.3% of the AEs were suspected to be study drug related and none of them were reported as SAEs. The subjects requiring dose adjustment/interruption was 5.8% and none of the subjects required additional therapy. None of the AEs led to discontinuations.

- Renal tubular disorders

No AESI of renal failure were noted in the granules group during the core or extension phase.

In the cross-over group during the extension phase, 5.8% of subject had AESI of renal tubular disorder, all of the events were suspected to be study drug related and 4.3% of the events were reported as SAEs. Study drug discontinuation were noted in 4.3% of subjects, 1 subject required dose adjustments/interruptions and 2 subjects required additional therapy.

- Acute renal failure

No AESI of renal failure were noted in the granules group during the core or extension phase.

In the cross-over group during the extension phase, 1 subject had nephropathy toxic which was suspected to be study drug related. This event led to dose adjustments/ interruptions but did not require additional therapy.

Details of increase in serum creatinine values based on laboratory data are discussed further below as part of clinical laboratory evaluation.

***Assessor's comment*:**

AESIs of Proteinuria were quite common throughout the entire granules period (40% to 60% of subjects with such events depending on the group) and often suspected to be study drug-related and led to dose adjustment in a third of subjects.

Regarding increased serum creatinine was less frequent (7.3% in the granules group and 5.8% in the crossover group), mostly required additional therapy and dose adjustment or interruption.

In the crossover group, three subjects (5.8%) had an AESI of renal tubular disorder suspected to be drug-related in 2 out of 3 cases. One patient required additional therapy.

A case of Acute renal failure suspected to be drug-related was reported in the crossover group during the extension phase and led to dose adjustment.

Severe cutaneous adverse reactions (SCARs)

In the granules group during the core or extension phase, 1 subject had an SAE of drug reaction with eosinophilia and systemic symptoms (DRESS) in the core phase, which was suspected to be study drug related and led to treatment discontinuation. The event was ongoing at the time of final examination and required additional therapy.

There were no AESI events of SCARs in the cross-over group during the extension phase.

Hearing loss

In the granules group during the core or extension phase, the number of subjects with hearing loss was low (4.5%; 5 subjects) and the suspected AEs was 0.9%. None of the hearing loss AESIs were considered as an SAE, none led to discontinuation of study drug or required additional therapy.

In the cross-over group during the extension phase, the number of subjects with hearing loss was low (7.2%; 5 subjects) and the suspected AEs was 4.3%. None of the hearing loss AESIs were considered as an SAE, none led to discontinuation of study drug or required additional therapy.

Peripheral blood cytopenias

In the granules group during the core or extension phase, the number of subjects with the AESI of peripheral blood cytopenias was low (6.4%; 7 subjects). Two subjects (1.8%) required dose adjustment or study-drug interruption, 4 subjects (3.6%) required additional therapy. None of the events were study drug related, serious or led to discontinuation.

In the cross-over group during the extension phase, the number of subjects with the AESI of peripheral blood cytopenias was low (7.2%; 5 subjects). Three subjects (4.3%) required additional therapy. None of the events were study drug related, SAEs, led to study drug discontinuation or required dose adjustment/interruption.

Gastrointestinal haemorrhage and ulcers; esophagitis

In the granules group during the core or extension phase, the number of subjects with the AESI of gastrointestinal haemorrhage was low (3.6%; 4 subjects), 2 subjects (1.8%) reported SAEs. This AESI led to discontinuation for 1 subject (0.9%), required dose adjustment or study-drug interruption in 1 subject (0.9%) and required additional therapy in 4 subjects (3.6%).

In the cross-over group during the extension phase, 3 subjects (4.3%) had an AESI of gastrointestinal haemorrhage. None of the AEs were suspected to be study drug related by the Investigator. One event

(gastrointestinal haemorrhage) was considered as an SAE. None of the events required dose adjustment/interruption or led to study drug discontinuation. Two subjects (2.9%) required additional therapy.

Lens opacities, retinal changes and optic neuritis

In the granules group during the core or extension phase, the number of subjects with the ocular AESI was low (1.8%; 2 subjects): one subject had lenticular pigmentation (in the core phase), retinal pigmentation and visual acuity tests abnormal (in the extension phase) and another subject had visual acuity reduced (in the core phase). The events retinal pigmentation and visual acuity tests abnormal were suspected to be study drug related by the Investigator and the event retinal pigmentation led to discontinuation of the study drug. None of the events were serious or required additional therapy. There were no cases with optic neuritis reported.

None of the AESIs of lens opacities, retinal changes and optic neuritis were reported in subjects in the cross-over group in the extension phase.

Ocular examinations are detailed in the next section as part of clinical laboratory evaluation.

***Assessor's comment*:**

SCARs: In the granules group, 1 SAE of DRESS was reported and suspected study drug-related.

Hearing loss: Few cases of hearing loss (5 subjects in each group) with no major safety impact, need for dose modification and additional therapy.

Peripheral blood cytopenias: None of the reported cases of peripheral blood cytopenias (7 subjects in the granules group (6.4%) and 5 subjects in the crossover group [7.2%] were suspected to be drug-related. Dose adjustment was required in 2 subjects of the granules group. Four subjects of the granules group and 3 subjects of the crossover group received additional therapy.

Gastrointestinal haemorrhage and ulcers; esophagitis: Some subjects presented an AESI of gastrointestinal haemorrhage (4 subjects in the granules group and 3 subjects in the crossover group). Additional therapy was required in 6 out 7 cases and there SAEs were reports (2 in the granules group, 1 in the crossover group), with one leading to treatment discontinuation.

Lens opacities, retinal changes and optic neuritis: Two patients in the granules group (1.8%) had presented at least one ocular AESI. Those non-serious events of lenticular or retinal pigmentation and reduced visual acuity were suspected to be drug-related. No additional therapy was required, as well as dose adjustment. Ocular examination will be discussed further below.

Overall, no new safety signals emerged from this data considering the known safety profile of deferasirox granules.

Clinical laboratory evaluation

Haematology

Table 16. Post-baseline laboratory values meeting specified criteria for notable/extended range during the entire granule period (Safety Set-4)

Laboratory parameter	Criteria for notable/extended ranges	DFX Cross -over N=69 n (%)	DFX Granule N=110 n (%)
Platelet count	Notable range: < 100	2 (2.9)	10 (9.1)
	Extended range: < 50	0	5 (4.5)
Absolute neutrophils	Notable range: < 1.5	6 (8.7)	23 (20.9)
	Extended range: < 0.5	0	2 (1.8)

Include all patients who fulfilled condition for each category.
Source: Tables 14.3-12.4, Table 14.3-13.4

Post-baseline notable values were noted for the following haematological parameters:

- Platelet count

In the granules group during the core or extension phase, post-baseline, 10 subjects (9.1%) had a platelet count within the notable range (<100×10^9/L). Of these, 8 subjects had a platelet count of ≥ 100×10^9/L, 1 subject had a platelet count of ≥ 50 to <100×10^9/L and 1 subject had the platelet count within the extended range (<50×10^9/L) at Baseline.

Out of 10 subjects, for 5 subjects (4.5%) the platelet count was in the extended range (<50×10^9/L). Of these, 3 subjects had a platelet count of ≥ 100×10^9/L, 1 subject had a platelet count of ≥ 50 to <100×10^9/L and 1 subject had a platelet count within the extended range <50×10^9/L at Baseline.

In the cross-over group during the extension phase, post-baseline 2 subjects (2.9%) had a platelet count within the notable range (<100×10^9/L). Both subjects had a platelet count of >100 x 10^9/L at Baseline. None of the subjects in the cross-over group had platelet count in extended range.

- Absolute neutrophils

Post-baseline in the granules group during the core or extension phase, 23 subjects (20.9%) had an absolute neutrophil count within the notable range (<1.5×10^9/L). Of these, 19 subjects had an absolute neutrophil count of ≥ 1.5×10^9/L and 4 subjects had an absolute neutrophil count of ≥ 0.5 to <1.5×10^9/L at Baseline.

Out of these 23 subjects, for 2 subjects (1.8%) the absolute neutrophil count was in extended range (< 0.5×10^9/L); of these, 1 subject had an absolute neutrophil count of ≥ 1.5×10^9/L and 1 subject had an absolute neutrophil count of ≥ 0.5 to <1.5×10^9/L at Baseline.

In the cross-over group during the extension phase, 6 subjects (8.7%) had an absolute neutrophil count within the notable range (<1.5×10^9/L). At Baseline the absolute neutrophil count of all these subjects was ≥ 1.5×10^9/L.

***Assessor's comment*:**

Notable values of haematology results (platelet counts and absolute neutrophils) provided in the CSR were not discussed. This purely descriptive report of haematological abnormal values is acknowledged and supported as most cases of thrombocytopenia and neutropenia were reported post-marketing, which makes it difficult to establish a causal relationship with exposure to deferasirox or with the underlying disease causing anaemia.

Clinical chemistry

Table 17. Post-baseline laboratory values meeting specified criteria for notable/extended range during the entire granule period (Safety Set-4)

Laboratory parameter	Criteria for notable/extended ranges	DFX DT Cross-over to DFX granules N=69 n (%)	DFX Granule N=110 n (%)
Serum creatinine	Notable range: Two consecutive values >ULN and >33% increase from Baseline	1 (1.4)	0
Creatinine clearance	Notable range: Two consecutive <60 mL/min	0	0
	Extended range: Two consecutive < 40 mL/min	0	0
ALT	Notable range: >5 x ULN and >2 x Baseline	4 (5.8)	21 (19.1)
	Extended range: >10 x ULN and >2 x Baseline value	1 (1.4)	3 (2.7)
AST	Notable range: >5 x ULN and >2 x Baseline	3 (4.3)	11 (10.0)
	Extended range: >10 x ULN and >2 x Baseline value	1 (1.4)	4 (3.6)

Includes all patients who fulfilled condition. i.e., subjects are also counted under notable range if they met the criteria for extended range
Source: Table 14.3-14.4, Table 14.3-15.4, Table 14.3-17.4, Table 14.3-18.4

Post-baseline notable values were noted for the following biochemistry parameters:

- Creatinine clearance

Post-baseline, no notable values were observed for creatinine clearance. However, in the cross-over treatment group 2 subjects had a worst post-baseline change to one value <40 mL/min:

• One subject had a single case of high creatinine and low creatinine clearance at Week 289 with no AEs documented by the Investigator as the subject did not have any symptoms; the creatinine values were normal at the subsequent visits.

• Another subject has been detailed in the Serum creatinine section below

- Serum creatinine

None of the subjects in the granules group had notable range in serum creatinine during the core or extension phase. In the cross-over treatment group during the extension phase, 1 subject reported a post-baseline shift to notable range in serum creatinine values at Week 305; however, this shift is attributed to a data error in the eCRF page; the creatinine values were normal at Week 305 as per central laboratory.

- ALT increase

Post-baseline in the granules group during the core or extension phase, 21 subjects (19.1%) had an ALT increase within notable range (>5×ULN and >2×Baseline value); of these, 13 subjects had an ALT ≤ ULN and 8 subjects had an ALT value within >ULN to ≤ 3×ULN range at Baseline. Of these 21 subjects, for 3 subjects (2.7%) the ALT increase was within extended range (>10×ULN and >2×Baseline value); of these, 1 subject had an ALT level of ≤ ULN and 2 subjects had an ALT level of >ULN to ≤ 3×ULN at Baseline.

Of the 21 subjects, 20 subjects had AEs which have been detailed in Section 14.3.3. For one subject the lab abnormality was considered clinically insignificant by the Investigator and no AE was reported.

In the cross-over group during the extension phase, post-baseline 4 subjects (5.8%) had an ALT increase within notable range (>5×ULN and >2×Baseline value); of these, 2 subjects had an ALT ≤ ULN and 2 subjects had ALT >ULN to ≤ 3×ULN at Baseline. Of these 4 subjects, for 1 subject (1.4%) ALT increase was within extended range (>10×ULN and >2×Baseline value); the subject had an ALT level ≤ ULN at Baseline.

- AST increase

Post-baseline in the granules group during the core or extension phase, 11 subjects (10.0%) had AST increase within notable range (>5×ULN and >2×Baseline value). Of these, 8 subjects had AST ≤ ULN and 3 subject had AST values within >ULN to ≤ 3×ULN at Baseline. Of these 11 subjects, for 4 subjects (3.6%) subjects AST was within extended range (>10×ULN and >2×Baseline value); of these 2 subjects had AST values ≤ ULN and 2 subjects had AST level values within > ULN to ≤ 3×ULN range at Baseline.

In the cross-over group, post-baseline during the extension phase, 3 subjects (4.3%) had AST increase within notable range (>5×ULN and >2×Baseline value); of these, 2 subjects had AST > ULN to ≤ 3×ULN range and 1 subject had AST ≤ ULN at Baseline. For 1 subject (1.4%) AST increase was within extended range (>10×ULN and >2×Baseline value); this subject had AST level ≤ ULN at Baseline.

- Hy's Law

A concurrent increase of ALT or AST > 3 × ULN and BILI (bilirubin) > 2 × ULN and ALP < 2 × ULN meeting Hy's law criteria was observed in 1 subject (1.4%) in the crossover group during the extension phase and 7 subjects (6.4%) in the granules group during the core or extension phase.

From the previous data cut-off of the EoC CSR (18-Jan-2021), 2 additional subjects in the granules group met the Hy's law criteria as detailed below:

• One subject (ICT pre-treated subject with Haemoglobin E disorder in granules group, 9 years old at enrollment) was noted with concurrent increase of ALT (>3 times ULN) and bilirubin (>2 times ULN) at Week 237, with ALP <ULN, ALT returned to normal range at unscheduled assessment at Week 239. Both increases were reported as moderate AEs of alanine aminotransferase increase and blood bilirubin increased and led to study discontinuation (suspected to be study drug related by the Investigator).

• Another subject (ICT naïve subject with sickle cell disease in granules group, 2 years old at enrollment) was noted with concurrent increase of ALT (>6 times ULN), AST (>14 times ULN) and bilirubin (>4 times ULN) with ALP <ULN, at single assessment on Week 289 and returned to normal range (ALT/AST) or improved (total Bilirubin) at subsequent assessment on Week 293 with no action taken to deferasirox treatment. AEs of transaminases increased, and blood bilirubin increased were noted which were not suspected to be study drug related by the Investigator.

Urinalysis

Table 18. Post-baseline laboratory values meeting specified criteria for notable/extended range during the entire granule period (Safety Set-4)

Laboratory parameter	Criteria for notable/extended ranges	DFX DT Cross-over to DFX granules N=69 n (%)	DFX Granule N=110 n (%)
Urinary protein/urinary creatinine ratio	Notable range: Two consecutive > 1.0 mg/mg	2 (2.9)	5 (4.5)

Includes all patients who fulfilled condition.
Source: Table 14.3-16.4

Post-baseline in the granules group during the core or extension phase, 5 subjects (4.5%) had urinary protein/urinary creatinine ratio within notable range (2 consecutive values >1.0 mg/mg); of these, the urinary protein/urinary creatinine ratio was ≤ 0.2 for 2 subjects and within range of > 0.2 to ≤ 0.5 for 2 subjects and > 1.0 for 1 subject at Baseline.

In the cross-over group during the extension phase, post-baseline 2 subjects (2.9%) had urinary protein/urinary creatinine ratio within notable range (2 consecutive values > 1.0 mg/mg); the urinary protein/urinary creatinine ratio was within range of > 0.2 to ≤ 0.5 for both subjects at Baseline.

In the granules group, at Baseline during the core or extension phase, 56 subjects (50.9%) had normal and 53 subjects (48.2%) had high urinary protein/creatinine ratio. Of the 56 subjects with normal urinary protein/creatinine ratio at Baseline, worst post-baseline shifts to high were reported in 46 subjects and shifts to high and low urinary protein/creatinine ratio was reported in 4 subjects.

In the cross-over group during the extension phase, at Baseline-ext, 30 subjects (43.5%) had normal and 39 subjects (56.5%) of subjects had high urinary protein/creatinine ratio. Of the 30 subjects with normal urinary protein/creatinine ratio at Baseline, worst post-baseline shifts to high urinary protein/creatinine ratio were reported in 26 subjects and worst post-baseline shifts to high and low urinary protein/creatinine ratio was reported in 2 subjects.

***Assessor's comment*:**

Serum creatinine/creatinine clearance: few notable values were reported in 2 subjects in the crossover group. The first subject had one with high then low creatinine clearance and the other with a post-baseline shift in serum creatinine attributed to a data error). None were associated to major clinical symptoms.

ALT/AST increase: ALT increase was reported in 21 subjects of the granules group and was classified as an AE in 20 out of 21 cases. In the crossover group, this event was reported in 4 subjects during the extension phase. AST increase was reported in 11 subjects in the granules group and 3 subjects in the crossover group during the extension phase. This is globally consistent with the number of AEs reported

Hy's Law: Since last data cut-off (21-Jan-2021), 2 additional subjects in the granules group met the Hy's Law criteria: one subject had a moderate AE of bilirubin increased that led to study discontinuation, suspected to be drug-related. The other one presented the same AEs but recovered within a week.

Urinalysis: no conclusion can be drawn for these purely descriptive data, overall consistent with the know safety profile of deferasirox granules.

Again, no new safety signals emerged from these data.

Vital signs, physical findings and other observations related to safety

Vital signs

Post-baseline, no clinically meaningful absolute change from Baseline in any of the vital signs were observed in any of the treatment groups.

***Assessor's comment*:**

No abnormalities of vital signs was reported during the entire granule period.

Ocular examinations

The details on subjects who completed all ocular examinations (visual acuity, fundus oculi, slit lamp and applanation tonometry), only three tests, only two and only one test at each time point for Safety Set-4 is provided in final CSR.

- Visual acuity

In the granules group during the core or extension phase, the proportion of subjects who had a complete distance visual acuity assessment were 89.1% (98 subjects) at Baseline, 53.6% (59 subjects) at Week 101, 38.2% (42 subjects) at Week 153, 30.0% (33 subjects) at Week 205, 27.3% (30 subjects) at Week 257, 21.8% (24 subjects) at Week 309 and 59.1% (65 subjects) at EOT-ext.

In the cross-over group during the extension phase, the proportion of subjects who had a complete distance visual acuity assessment were 88.4% (61 subjects) at Baseline, 75.4% (52 subjects) at Week

101, 58.0% (40 subjects) at Week 153, 44.9% (31 subjects) at Week 205, 37.7% (26 subjects) at Week 257, 36.2% (25 subjects) at Week 309 and 85.5% (59 subjects) at EOT-ext.

Change from baseline in LogMAR score categories by baseline LogMAR score categories during the extension phase is summarized in final CSR.

INCREASE IN logMAR SCORE

At any time point post-baseline, increase in logMAR score of ≥ 0.2 indicating clinically relevant worsening in visual acuity was reported in 8 subjects (7.3%) in the granules group in the core or extension phase and 3 subjects (4.3%) in the cross-over group in the extension phase.

Table 19. Categorical analysis of logMAR score (increase) for worst eye during the entire granule period (Safety Set-4)

Change from Baseline	DFX Cross-over N = 69 n (%)	DFX Granule N = 110 N (%)
Worst post-baseline changes*		
<0.1	43 (62.3)	67 (60.9)
≥0.1 to <0.2	4 (5.8)	6 (5.5)
≥0.2 to <0.3	0	2 (1.8)
≥0.3 to <0.6	3 (4.3)	5 (4.5)
>0.6	0	1 (0.9)
Not evaluable	0	1 (0.9)
Missing baseline assessment	3 (4.3)	8 (7.3)
Missing post-baseline assessment	4 (5.8)	0
Missing both baseline and post-baseline assessment	6 (8.7)	13 (11.8)
No increase from baseline	6 (8.7)	7 (6.4)

Not evaluable patients are those who had any post-baseline assessment performed using different conditions to baseline.

*All categories are mutually exclusive

Source: Table 14.3-22.4

Of the 11 subjects with increase in logMAR score of ≥ 0.2 post-baseline, 4 subjects had abnormalities of amblyopia (1 subject), myopia (2 subjects), and bilateral visual acuity reduced (1 subject) which were deemed as clinically significant by the Investigator. None of these abnormalities were suspected to be study drug related by the Investigator:

• Subject (ICT pre-treated subject in the granules group, 6 years old): increase in logMAR score was noted from -0.10/0.20 (right eye/ left eye; with correction) at Baseline, to 0.60/0.20 (with correction) at Week 25, and was 0.30/0.30 (with correction) at EOT-core. The event amblyopia of right eye was reported in medical history and ongoing at Screening and Week 25 visits.

• Subject (ICT naive subject in the granules group, 9 years old) increase in logMAR score was noted from 0.30/0.12 (without correction) at Baseline to 0.48/0.48 (without correction) at Week 101. AE of myopia was reported not suspected to be study drug related by the Investigator.

• Subject (ICT pre-treated subject in the granules group, 9 years old): increase in logMAR score was noted from 0.18/0.10 (without correction) at Baseline to 0.30/0.10 (without correction) at Week 25, to 0.40/0.30 (without correction) at EOT-core. AE of myopia was reported, not related to study treatment per the Investigator assessment, and the subject was prescribed glasses. It was reported that after correction with glasses, visual acuity was normal (logMAR score of 0.0).

• Subject (ICT pre-treated in the granules group, 7 years old): increase in logMAR score was noted from 0.18/0.30 (without correction) at Baseline and 0.18/0.30 (with correction for right eye) Week 25, to 0.70/0.48 (without correction) at EOT-core. An AE of (bilateral) visual acuity reduced was reported, not related to study treatment per Investigator assessment. It was reported that clinician discussed eyeglasses with the subject and parents.

Additionally, one subject had a clinically significant change in logMAR score but no worsening from Baseline was observed:

• Subject (ICT pre-treated subject in the granules group, 4 years old) had a clinically significant change in logMAR score noted from 0.30/0.48 (with correction) at Baseline to 0.48/0.48 (without correction) at Week 25 and improved to 0.30/0.18 (with correction) at EOT-core. There was no worsening of logMAR score from Baseline observed. This subject had corresponding AEs of visual acuity tests abnormal and retinal pigmentation of mild severity from Day 394 (EOT-ext) onwards; both AEs were suspected to be study drug related by the Investigator. The AE of retinal pigmentation led to discontinuation from study.

Subjects who had post-baseline increase in logMAR score of ≥ 0.2 which were considered insignificant by the Investigator have been detailed below. No AEs were reported in these 7 subjects, in majority of them logMAR score improved or returned to baseline score at subsequent assessments, in 2 subjects persisted at the time of final examination (Listing 16.2.9-4.4):

• Subject (ICT pre-treated subject in the cross-over group, 3 year old) increase in logMAR score was noted from 0.10/0 (without correction) at Baseline to 0.30/0.30 (without correction) at Week 101 and improved to 0.10/0.10 (without correction) at Week 205, 0/0.10 (without correction) at Week 257 and EOT-Ext visit.

• Subject (ICT pre-treated subject in the cross-over group, 2 years old) increase in logMAR score was noted from 0.18/0.18 (without correction) at Baseline to 0.30/0.30 (without correction) at Week 25, 0.18/0.60 (without correction) at EOT-core, 0.48/0.48 (without correction) at Week 101 and improved to 0.30/0.30 (without correction) at Week 153 and EOT-ext.

• Subject (ICT pre-treated subject in the cross-over group, 15 years old) increase in logMAR score was noted from 0/0 (without correction) at Baseline to 0.48/0 (without correction) at Week 153 and returned to 0/0 (without correction) at Week 205. At Week 257, an increase was noted to 0.18/0 (without correction) and returned to normal by the EOT-Ext visit.

• Subject (ICT pre-treated subject in the granules group, 9 years old) increase in logMAR score was noted from 0.30/0.10 (without correction) at Baseline to 0.40/0.40 (without correction) at Week 101 and was maintained at 0.40/0.40 (without correction) at an unscheduled visit and EOT-ext.

• Subject (ICT naive subject in the granules group, 2 years old) increase in logMAR score was noted from 0/0 (without correction) at Baseline to 0.30/0.30 (without correction) at Week 101 and returned to 0/0 (without correction) at Week 153 which was maintained at week 257 and EOT-ext.

• Subject (ICT pre-treated in the granules group, 3 years old): increase in logMAR score was noted from 0.10/0.10 (without correction) at Baseline to 0.18/0.30 (without correction) at Week 25, to 0.20/0.20 (with correction) at EOT-core.

• Subject (ICT pre-treated subject in the granules group, 9 years old) increase in logMAR score was noted from 0/0 (without correction) at Baseline to 0/0.30 (without correction) at Week 153 and returned to 0/0 (without correction) at Week 205, week 257 and EOT-ext.

One additional subject had post-baseline increase in logMAR score of ≥ 0.2 which occurred more than 30 days after the last treatment:

• Subject (ICT naive subject in the granules group, 2 years old): an increase in the logMAR score was noted from 0.50/0.50 (without correction) at Baseline to 1/1 (without correction) at EOT-Ext (Day 2199). Visual acuity with correction was reported at Week 205 (0.40/0.30) and Week 257 (0.18 both eyes). This change at EOT-ext visit was not considered clinically significant or related to study medication, per Investigator, the subject had myopia and visual acuity with correction was 0.18/0.18 for both eyes, no ocular-related AEs were reported.

DECREASE IN logMAR SCORE

Subjects who had an improvement in the logMAR score post-baseline has been summarized in the table below.

Table 20. Categorical analysis of logMAR score (decrease) for worst eye during the entire granule period (Safety Set-4)

Change from Baseline	DFX Cross-over N = 69 n (%)	DFX Granule N = 110 N (%)
Best post-baseline changes		
<0.1	8 (11.6)	8 (7.3)
≥0.1 to <0.2	5 (7.2)	5 (4.5)
≥0.2 to <0.3	1 (1.4)	2 (1.8)
≥0.3 to <0.6	3 (4.3)	9 (8.2)
>0.6	0	0
Not evaluable	0	1 (0.9)
Missing baseline assessment	3 (4.3)	8 (7.3)
Missing post-baseline assessment	4 (5.8)	0
Missing both baseline and post-baseline assessment	6 (8.7)	13 (11.8)
No decrease from baseline	39 (56.5)	64 (58.2)

Not evaluable patients are those who had any post-baseline assessment performed using different conditions to baseline.
Source: Table 14.3-22.4

Assessor's comment:

The number of subjects completed distance visual acuity assessment was variable throughout the study (from 24 to 98 subjects in the granules group and from 25 to 61 subjects in the crossover group), which makes it complicated to draw any meaningful conclusions. In the safety set-3, increase from baseline in logMAER score was reported in 4 subjects in the granules group and 1 subject in the DT group. During the entire granule period (safety set-4), worsening in visual acuity (defined as increase in logMAR score ≥ 0.2) was reported in 8 subjects (7.3%) in the granules group and 3 subjects in the crossover group (4.3%) in the crossover group in the extension phase.

Per Investigator's assessment, 4 subjects (all in the granules group and aged ≤ 9 years old) presented clinically significant AE: amblyopia (1 subject), myopia (2 subjects) and bilateral visual acuity reduced (1 subject). None of these abnormalities were considered drug-related. One subject had a clinically significant change in logMAR score with a mild AE of retinal pigmentation that led to study discontinuation. This event was suspected to be drug-related.

The other cases (8 subjects) were not associated to any AE. In 5 out of 8 cases, logMAR score improved or returned to baseline. The number of subjects with improvement in logMAR score was provided but corresponding results were not discussed.

- Applanation tonometry

In the granules group during the core or extension phase, the proportion of subjects who had a complete applanation tonometry assessment were 73.6% (81 subjects; left eye) and 72.7% (80 subjects; right eye) at Baseline, 47.3% (52 subjects) at Week 101, 34.5% (38 subjects) at Week 153, 24.5% (27 subjects) at Week 205, 24.5% (27 subjects) at Week 257, 19.1% (21 subjects) at Week 309 and 54.5% (60 subjects) at EOT-ext in the granules group.

In the cross-over group during the extension phase, the proportion of subjects who had a complete applanation tonometry assessment were 79.7% (55 subjects) at Baseline-ext, 65.2% (45 subjects) at Week 101, 50.7% (35 subjects) at Week 153, 37.7% (26 subjects) at Week 205, 36.2% (25 subjects) at Week 257, 29.0% (20 subjects) at Week 309 and 78.3% (54 subjects) at EOT-ext.

The intraocular pressure shift (from >5 to ≤ 21, >21 to ≤30 and > 30 at post-baseline or vice-versa) during the granule period for Safety Set-4 is presented in final CSR. The change from Baseline in intraocular pressure by visit for Safety Set-4 is provided in final CSR.

INCREASE IN IOP VALUES

Majority of the subjects in the granules group (80.0%) and the cross-over group (76.8%) had normal IOP (values >5 to ≤21 mmHg) post-baseline.

Increase from baseline ≥ 5 mmHg and < 10 mmHg was reported in 20.0% of subjects in the granules group during the core or extension phase and 15.9% of subjects in the cross-over group in the extension phase. None of the subjects had ≥ 10 mmHg increase from baseline.

Table 21. Categorical analysis of intraocular pressure for worst eye during the entire granule period (Safety Set 4)

Change from Baseline	DFX Cross-over N = 69 n (%)	DFX Granule N = 110 N (%)
At least one Post-baseline absolute value ≤5 mmHg	0	0
At least one Post-baseline absolute value >5 to ≤21 mmHg	53 (76.8)	88 (80.0)
At least one Post-baseline absolute value >21 to ≤30 mmHg	2 (2.9)	6 (5.5)
At least one Post-baseline absolute value >30 mmHg	0	0
Worst increase in Post-baseline values		
Increase from baseline ≥5 mmHg and <10 mmHg	11 (15.9)	22 (20.0)
Increase from baseline ≥10 mmHg	0	0

Source: Table 14.3-26.4

At least one post-baseline absolute value of >21 to ≤ 30 mmHg was reported in 6 subjects (5.5%) in the granules group which have been detailed below.

• Subject (ICT naive subject, 7 years old) had an increase in intraocular pressure from 18 mmHg at Baseline to 24 mmHg at Week 101 that was considered as clinically significant by the Investigator and decreased to 20 mm Hg at EOT-extension. The subject had an AE of ocular hypertension (mild) on Day 707 that resolved in 408 days.

• Subject (ICT pre-treated subject, 5 years old) had a clinically insignificant increase in intraocular pressure to 22 mmHg in the left eye at Week 101.

• Subject (ICT pre-treated subject, 2 years old) had a clinically insignificant increase in intraocular pressure to 25 mmHg in both eyes at EOT-Ext.

• Subject (ICT naive subject, 2 years old) had a clinically insignificant increase in intraocular pressure to 22 mmHg in both eyes at Week 101.

• Subject (ICT pre-treated subject, 7 years old) had a clinically insignificant increase in intraocular pressure to 22 mmHg in left eye at Week 25.

• Subject (ICT pre-treated subject, 9 years old) had a clinically insignificant increase in intraocular pressure to 23 mmHg in both eyes at Week 25.

At least one post-baseline absolute value of >21 to ≤ 30 mmHg was reported in 2 subjects (2.9%) in the cross-over group which have been detailed below:

• Subject (ICT pre-treated subject, 5 years old) had an increase in intraocular pressure from 20 mmHg at Baseline to 24 mmHg at Week 257 that was considered as clinically significant by the Investigator. It decreased to 14 mmHg by EOT-Extension. The subject had an AE of ocular hypertension (mild) on Day 1827 that resolved in 33 days.

• Subject (ICT pre-treated subject, 3 years old) had an increase in intraocular pressure to 22 mmHg in the left eye at Week 101, with Investigator overall interpretation as 'normal'.

DECREASE IN IOP VALUES

Decrease in IOP from Baseline was noted as follows:

• Decrease of ≥5 mmHg and <10 mmHg from Baseline was reported in 21 subjects (19.1%) in the granules group and 8 subjects (11.6%) in the cross-over group.

• Decrease of ≥10 mmHg from Baseline was reported in 2 subjects (1.8%) in the granules group and 1 subject (1.4%) in the cross-over group.

Assessor's comment:

Again, the number of subjects who completed the applanation tonometry assessment fluctuate during study in both groups. Since last data cut-off, more subjects aged ≤9 years old had at least one post-baseline value >21 to ≤31 mmHg: 2 patients in the crossover group and 6 patients in the granules group (compared to 2 subjects in each treatment arm).

During the entire granule period, the increase of intraocular pressure was deemed clinically significant in 5 out of 6 cases in the granules group. The last subject had a mild AE of ocular pressure that resolved in 408 days. In the crossover group, one of the two patients with increased intraocular pressure had an AE of ocular hypertension that resolved in 33 days. Decrease in IOP values were provided but not discussed.

- Slit lamp examination

In the granules group during the core and extension phase, the proportion of subjects who had a complete slit lamp assessment for both left and right eyes were 99.1% (109 subjects) at Baseline, 54.5% (60 subjects) at Week 101, 39.1% (43 subjects) at Week 153, 30.0% (33 subjects) at Week 205, 28.2% (31 subjects) at Week 257, 22.7% (25 subjects) at Week 309 and 61.8% (68 subjects) at EOT-ext in the granules group.

In the cross-over group during the extension phase, the proportion of subjects who had a complete slit lamp assessment for both left and right eyes were 100% (69 subjects) at Baseline-ext, 81.2% (56 subjects) at Week 101, 60.9% (42 subjects) at Week 153, 44.9% (31 subjects) at Week 205, 39.1% (27 subjects) at Week 257, 36.2% (25 subjects) at Week 309 and 88.4% (61 subjects) at EOT-ext .

Post-baseline abnormalities during the extension phase have been summarized below.

Table 22. Post-baseline abnormality in slit lamp during the extension phase (Safety Set 4)

Visit	Abnormality	Eye	DFX Cross-over N=69 n (%)	DFX Granule N = 110 n (%)
Evaluation: Conjunctiva				
Week 101	Significant	Right	0	1 (0.9)
		Left	0	1 (0.9)
	Insignificant	Right	1 (1.4)	0
		Left	1 (1.4)	0
EOT - EXT	Significant	Right	0	1 (0.9)
		Left	0	1 (0.9)
	Insignificant	Right	2 (2.9)	0
		Left	2 (2.9)	0
Evaluation: Cornea				
Week 101	Significant	Right	0	1 (0.9)
		Left	0	1 (0.9)
	Insignificant	Right	2 (2.9)	0
		Left	1 (1.4)	0
EOT - EXT	Insignificant	Right	2 (2.9)	0
		Left	1 (1.4)	0
Evaluation: Cristallin				
Week 101	Insignificant	Right	2 (2.9)	0
		Left	1 (1.4)	0
Week 257	Insignificant	Right	1 (1.4)	0
		Left	1 (1.4)	0
Week 309	Insignificant	Right	1 (1.4)	0
		Left	1 (1.4)	0
EOT - EXT	Insignificant	Right	2 (2.9)	0
		Left	2 (2.9)	0
Evaluation: Iris				
Week 101	Insignificant	Right	1 (1.4)	1 (0.9)
		Left	0	1 (0.9)
Week 153	Insignificant	Right	0	1 (0.9)
		Left	0	1 (0.9)
EOT-EXT	Insignificant	Right	0	1 (0.9)
		Left	0	1 (0.9)
Evaluation: Lens				
Week 101	Insignificant	Right	2 (2.9)	0
		Left	2 (2.9)	0
Week 153	Insignificant	Right	1 (1.4)	0
Week 205	Insignificant	Right	0	1 (0.9)
		Left	0	1 (0.9)
EOT-EXT	Insignificant	Right	1 (1.4)	1 (0.9)
		Left	1 (1.4)	1 (0.9)
Evaluation: Lids				
Week 101	Significant	Right	1 (1.4)	1 (0.9)
		Left	1 (1.4)	1 (0.9)
EOT-EXT	Significant	Right	1 (1.4)	0
		Left	1 (1.4)	0

Evaluation: Sclera				
Week 101	Insignificant	Right	1 (1.4)	0
Week 153	Insignificant	Right	1 (1.4)	0
EOT-EXT	Insignificant	Right	1 (1.4)	0

Visits are displayed if at least one subject has an abnormality finding at that visit.
Source: Table 14.3-23.4

Post-baseline, majority of the subjects did not have clinically significant abnormalities as deemed by the Investigator except for 3 subjects (2 in the granules group and 1 in the cross-over group) who had significant abnormalities of conjunctiva (conjunctivitis in 1 subject), cornea (punctate epithelial erosion in 1 subject) and lids (epiblepharon and chalazion, in 1 subject each) in slit lamp examinations. None of these abnormalities were suspected to be study drug related by the Investigator. These abnormalities have been detailed below:

• Subject (ICT-naive subject in the granules group, 2 years old) was noted to have a clinically insignificant abnormality in conjunctiva of both eyes at Week 25, EOT-core (Day 357) and was assessed as significant at EOT-ext (Day 741). The subject had AEs of conjunctivitis not suspected to be study drug related by the Investigator and the AEs resolved in 5 days. The slit lamp examination indicated normal eye conjunctiva at Screening.

• Subject (ICT pre-treated subject in the granules group, 4 years old) was noted to have clinically significant abnormalities of punctate epithelial erosion and epiblepharon on examination of the cornea and lids for both the eyes at Week 101 (AEs of acquired epiblepharon and punctuate keratitis that resolved in 21 days, both not suspected to be study drug related by the Investigator). The slit lamp examination indicated normal cornea at Baseline.

• Subject (ICT-naive subject in the cross-over group, 4 years old) had clinically significant abnormality of chalazia in both eye lids at EOT-core (AE of chalazion that resolved in 18 days) and upper lid chalazia in both eye lids at EOT-ext (AE of chalazion that was ongoing at the time of final examination). Both AEs were not suspected to be study drug related by the Investigator. This subject also had clinically insignificant abnormality in right eye iris and left eye conjunctiva and cornea at Baseline, and left eye cornea at Week 25.

A total of 23 subjects (14 in the granules group in the core or extension phase and 9 subjects in the crossover group in the extension phase) had any baseline and/or post-baseline abnormality reported for slit lamp exam, considered not clinically significant by the Investigator. These included abnormalities of conjunctiva (7 subjects), cornea (2 subjects), cristallin (4 subjects), iris (7 subjects), lens (7 subjects), lids (4 subjects), sclera (3 subjects). Of the 23 subjects, 7 subjects reported AEs related to slit lamp examination findings. Twenty subjects had post-baseline abnormalities which have been detailed below:

• Subject (ICT-naive subject in the cross-over group, 2 years old) had clinically insignificant abnormality in both eye lids at Baseline. The subject had AEs of hordeolum on Day 89, Day 128 and Day 309 that resolved in 18 days, 173 days and 50 days respectively. The subject had AEs of hordeolum (stye) on Day 414 and myopia on Day 449 that were ongoing at the time of data cut-off.

• Subject (ICT naive subject in the cross-over group, 6 years old) had clinically insignificant abnormality (not specified) in cristallin both eyes at Week 257 and EOT-ext.

• Subject (ICT pre-treated subject in the cross-over group, 5 years old) had clinically insignificant abnormality of dry eyes at the EOT-Ext visit.

• Subject (ICT-naive subject in the cross-over group, 2 years old) had clinically insignificant abnormality in right eye cristallin and both eye lens (very early cataract in both eyes) at Week 101 only, no lens abnormality reported at subsequent assessments at Week 153 and EOT-ext.

• Subject (ICT-naive subject in the cross-over group, 9 years old) had clinically insignificant abnormality in right eye iris (naevus) at Week 101.

• Subject (ICT pre-treated subject in the cross-over group, 3 years old) had clinically insignificant abnormality in right eye sclera (pigmentary changes over sclera) at Week 25, EOT-core, Week 101, Week 153 and at EOT-ext. The subject did not have any abnormality at Baseline. The subject had an AE of scleral pigmentation (mild, suspected to be study drug related by Investigator) on Day 356 that resolved on Day 1310. The subject also had insignificant lens abnormality reported at single visit (Week 153).

• Subject (ICT pre-treated subject in the cross-over group, 9 years old) had clinically insignificant abnormality in conjunctiva, cornea, lens (pseudophakia, artificial intraocular lens), residual exotropia at Baseline which continued until the EOT-Ext visit and cristallin at Week 25 which continued until EOT-Ext visit. The subject had an AE of retinal tear in the core phase.

• Subject (ICT pre-treated subject in the cross-over group, 3 years old) had clinically insignificant abnormality of cornea of right eye at Week 101 and EOT-ext (per Investigator, the subject had a clear cornea with 2 faint endothelial thickening, possible posterior polymorphous dystrophy). This subject also had insignificant abnormality of conjunctiva both eyes at EOT-Ext (mild conjunctival papillae). No abnormalities were noted at Baseline.

• Subject (ICT pre-treated subject in the cross-over group, 3 years old) had clinically insignificant abnormality (not specified) in both eyes iris at Baseline which was normal at the subsequent visits. In addition, the subject had AE of hordeolum reported on Day 976 that resolved in 27 days. This subject had a medical history of heterochromia iridis.

• Subject (ICT pre-treated subject in the granules group, 9 years old) had a clinically insignificant abnormality (unknown) of conjunctiva at EOT-Core visit.

• Subject (ICT pre-treated subject in the granules group, 4 years old) had an AE of lenticular pigmentation reported on Day 29 that was ongoing at the time of final examination. The subject had clinically insignificant abnormality in left eye cristallin and minimal pigment on lens surface at the final examination.

• Subject (ICT naive subject in the granules group, 2 years old) had congenital right eye brown syndrome recorded at Week 25 and subsequent assessments that was not clinically significant.

• Subject (ICT pre-treated subject in the granules group, 13 years old) had clinically insignificant abnormality in both eyes' iris (iris normal with thin filamentous persistent pupillary membrane (PPM)) at Baseline which continued until EOT-Ext visit.

• Subject (ICT pre-treated subject in the granules group, 14 years old) had clinically insignificant abnormality in conjunctiva, eye lids, sclera, and mild posterior blepharitis at EOT-core, these were reported normal at subsequent Week 101 assessment. In addition, the subject had an AE of keratopathy (contact lens related keratopathy) on Day 623 that resolved in 5 days.

• Subject (ICT pre-treated subject in the granules group, 15 years old) had clinically insignificant abnormality at Baseline in the left eye iris (not specified) and left eye lens at Week 25 (mild posterior subcapsular cataract per Investigator), subsequent assessments of lens until EOT-ext reported normal.

• Subject (ICT pre-treated subject in the granules group, 9 years old) had clinically insignificant abnormality of both eyes lens at Baseline and Week 25 (mild posterior subcapsular cataract per Investigator), and at Week 205 and EOT-Ext (tiny haze near posterior capsular per Investigator).

• Subject (ICT pre-treated subject in the granules group, 12 years old) had clinically insignificant abnormality of conjunctiva (mild allergic conjunctivitis) in both eyes at Week 205.

• Subject (ICT naive subject in the granules group, 2 years old) had clinically insignificant abnormality in the iris of left eye (dilates poorly) at EOT-core.

• Subject (ICT pre-treated subject in the granules group, 7 years old) had an AE of eye allergy on unknown date which was ongoing at the time of final examination and moderate conjunctivitis on Day 158. The subject had clinically insignificant abnormality of lids on both eyes at EOT-Core.

• Subject (ICT pre-treated subject in the granules group, 9 years old) in the granules group had clinically insignificant abnormality in the conjunctiva and sclera of both eyes at Week 25 (mild papillary reaction) (AEs of conjunctivitis allergic and myopia) which were ongoing at the time of the final visit. The subject had mild papilla consistent with allergic conjunctivitis in the right eye lid and mild papilla due to allergies in the left eye lid at EOT-core. No abnormalities were noted at Baseline.

• Subject (ICT pre-treated subject in the granules group, 7 years old) had clinically insignificant abnormality in the iris of right eye (small persistent pup membrane attached to anterior capsule) reported at Week 25 and EOT-core (Day 329). This subject also had worsening in visual acuity at EOT-core visit (0.70/0.48 without correction) and an AE of (bilateral) visual acuity reduced was reported, not related to study treatment per Investigator assessment. It was reported that clinician discussed eyeglasses with the subject and parents.

Three subjects had abnormalities (not specified) only at Baseline visit.

Assessor's comment:

Per investigator's assessment, only 3 subjects aged ≤4 years (2 in the granules group 1 in the crossover group) had clinically significant abnormalities that were not considered drug-related by investigators. AEs of conjunctivitis, acquired epiblepharma and punctuate keratitis that occurred in subjects of the granules group resolved after 21 days at most. The subject in the crossover group had chalazia in both eye lids at EOT-core that resolved in 18 days and then again upper lid chalazia in both eye lids again at EOT-ext.

Among the 23 subjects aged ≤15 years old (14 in the granules group and 9 in the crossover group) who had any baseline and/or post-baseline abnormalities deemed insignificant.

Eight subjects in the granules group and 6 subjects in the crossover group presented such abnormalities at the time of their final examination (EOT-core, EOT-ext or ongoing AEs at the last data cut-off). The three remaining subjects presented abnormalities solely at baseline.

- Fundus oculi examination

In the granules group during the core or extension phase, the proportion of subjects who had a complete fundus oculi assessment were 95.5% (105 subjects) at Baseline, 52.7% (58 subjects) at Week 101, 36.4% (40 subjects) at Week 153, 23.6% (26 subjects) at Week 205, 26.4% (29 subjects) at Week 257, 19.1% (21 subjects) at Week 309 and 59.1% (65 subjects) at EOT-ext in the granules group.

In the cross-over group during the extension phase, the proportion of subjects who had a complete fundus oculi assessment were 100% (69 subjects) at Baseline-ext, 81.2% (56 subjects) at Week 101, 58.0% (40 subjects) at Week 153, 39.1% (27 subjects) at Week 205, 36.2% (25 subjects) at Week 257, 33.3% (23 subjects) at Week 309 and 88.4% (61 subjects) at EOT-ext.

Post-baseline abnormalities during the extension phase have been summarized in the table below.

Table 23. Post-baseline abnormality in fundus oculi during the extension phase (Safety Set 4)

Visit	Abnormality	Eye	DFX Cross-over N=69 n (%)	DFX Granule N = 110 n (%)
Week 101	Insignificant	Right	0	0
		Left	1 (1.4)	0
	Significant	Right	0	0
		Left	0	0
Week 205	Insignificant	Right	0	0
		Left	0	1 (0.9)
	Significant	Right	0	0
		Left	0	0
Week 257	Insignificant	Right	0	4 (3.6)
		Left	0	3 (2.7)
	Significant	Right	0	0
		Left	0	0
Week 309	Insignificant	Right	0	1 (0.9)
		Left	0	1 (0.9)
	Significant	Right	0	0
		Left	0	0
EOT-Ext	Insignificant	Right	0	2 (1.8)
		Left	1 (1.4)	1 (0.9)
	Significant	Right	0	1 (0.9)
		Left	0	1 (0.9)

Visits are displayed if at least one subject has an abnormality finding at that visit.
Source: Table 14.3-28.4

Post Baseline, majority of the subjects did not have clinically significant fundus oculi abnormalities in the extension phase except 1 subject in the granules group, detailed below.

• Subject (ICT pre-treated subject in the granules group, 4 years old) had clinically significant abnormality of pigmentary changes over fundus of both eyes at EOT-ext. The fundus oculi examination was normal at Screening. This subject had AEs of astigmatism and myopia at Baseline and AE of lenticular pigmentation (mild, not suspected to be study drug related by the Investigator) from Day 29 onwards. The change in logMAR score was noted from 0.30/0.48 (with correction) at Baseline to 0.48/0.48 (without correction) at Week 25 and improved to 0.30/0.18 (with correction) at EOT-core (considered clinically significant by Investigator) (Listing 16.2.9-4.2). This subject had corresponding AEs of visual acuity tests abnormal and retinal pigmentation of mild severity from Day 394 (EOT-ext) onwards; both AEs were suspected to be study drug related by the Investigator. The AE of retinal pigmentation led to discontinuation from study.

A total of 14 subjects (10 in the granules group and 4 subjects in the crossover group) had any abnormalities at Baseline and/or post-baseline which were considered clinically insignificant by the Investigator. The common findings observed were large cupping disc (2 subjects). Eleven subjects had normal Baseline and only had post-baseline abnormalities which have been detailed below:

• Subject (ICT pre-treated subject in the cross-over group, 9 years old) had an AE of retinal tear on Day 57 and was resolved in 36 days during the core phase which was not suspected to be study drug related. The subject also had clinically insignificant abnormalities (not specified) at Week 101 and EOT-Ext visit during the extension phase.

• Subject (ICT pre-treated subject in the granules group, 5 years old) had a clinically insignificant abnormality in the right eye at Week 257 (stable temporal atrophy right optic disc). No abnormalities reported at subsequent visits.

• Subject (ICT naive subject in the granules group, 6 years old) had a clinically insignificant abnormality in both eyes at Week 25 (temporal disc pallor). No abnormalities reported at subsequent visits.

• Subject (ICT naive subject in the granules group, 2 years old) had a clinically insignificant abnormality in right eye at Week 25 (not specified).

• Subject (ICT pre-treated subject in the granules group, 14 years old) had clinically insignificant abnormalities in both eyes at Baseline, Week 25 (not specified) and EOT-Core visit (mild tigroid background of retina).

• Subject (ICT naive subject in the granules group, 2 years old) had a clinically insignificant abnormality in both eyes at Week 25 (not specified), no abnormal findings reported at subsequent assessments.

• Subject (ICT naive subject in the granules group, 4 years old) had a clinically insignificant abnormalities in both eyes at Week 25, Week 257 and EOT-Ext visit (large cupping eyes).

• Subject (ICT naive subject in the granules group, 5 years old) had a clinically insignificant abnormality in the left eye at Week 205 and Week 257, right eye at Week 257 (large cupping disc). No abnormalities reported at subsequent visits.

• Subject (ICT pre-treated subject in the granules group, 9 years old) had a clinically insignificant abnormality in both eyes at Week 257 (mild tilted disc). No abnormalities reported at subsequent visits.

Five subjects had clinically insignificant abnormalities which were noted only at the Baseline visit, none of the subjects reported any AEs:

Assessor's comment:

As of 18 January 2021, 2 subjects in the DT group had significant fundus oculi examinations, both mild and not related to treatment. During the entire granule period, one subject in the granules group with baseline AEs of astigmatism and myopia, had a mild AE of lenticular pigmentation from Day 29 onwards. This subject then had an AE of retinal pigmentation that led to treatment discontinuation (already discussed above). Among the 14 subjects (10 in the granules group and 4 in the crossover group) aged ≤ 14 years with clinicallay insignificant abnormalities, 5 subjects presented such abnormalities at baseline and only one subject in the crossover group had an associated AE of retinal tear that resolved in 36 days.

The potential causal relationship with study treatment was not discussed for these results.

- Lens opacities classification system III and color fundus photography (independent review by central reader)

Protocol amendment 6 was implemented to introduce the requirement for central collection and assessment of photographs (retrospective and prospective) from ocular examinations (lens photographs and wide-angle fundus photographs) collected during the study. The central reading of ocular images was done in accordance with independent review charter. The central reader assessment of photographs and the local ophthalmologist examination during the on-site visits, were done independently.

Images which were considered "cannot grade" as per the central reader's assessments could not be graded and assessed for the presence of any abnormality. If the confidence score was 'cannot grade' or 'not available' for slit lamp or CFP images from a given eye, the grader would not be able to complete the abnormal findings assessment of the given eye and the assessment would be grayed out or hidden on the imaging CRF. Some sites only had PDF copies of images filed, which were not evaluable. Thus, the number of subjects with completed LOCSIII or color fundus photography assessments are lower than number of subjects who had sent any image for central reading.

As both of these assessments were only collected since Protocol Amendment 6 (which was implemented after the EoC CSR), the analysis was also performed for Safety Set-1 (all ICT-naive subjects who received at least one dose of the study drug during the core phase), Safety Set-2 (all ICT pre-treated subjects

who received at least one dose of study drug during the core phase) and Safety Set-3 (all subjects who received at least one dose of study drug during the core phase).

SAFETY SET-3

In Safety Set-3, the number of subjects who completed both assessments (LOCSIII and color Fundus photography) have been summarized below.

Table 24. Number of patients with LOCSIII and/or color fundus photography during the core phase (Safety Set-3)

Timepoint	Examination	DFX DT N = 111 n (%)	DFX Granule N = 110 n (%)
Baseline	2 assessments completed	18 (16.2)	18 (16.4)
	Only one assessment completed	25 (22.5)	13 (11.8)
	Missing assessments	68 (61.3)	79 (71.8)
Week 25	2 assessments completed	25 (22.5)	23 (20.9)
	Only one assessment completed	10 (9.0)	8 (7.3)
	Missing assessments	76 (68.5)	79 (71.8)
EOT-Core	2 assessments completed	26 (23.4)	18 (16.4)
	Only one assessment completed	11 (9.9)	13 (11.8)
	Missing assessments	74 (66.7)	79 (71.8)

An examination is considered completed when both eyes are completed with an image quality of High or Borderline

Source: Table 14.3-30.11

SAFETY SET-4

In Safety Set-4, the number of subjects who completed both assessments (LOCSIII and color Fundus photography) have been summarized below.

Table 25. Number of patients with LOCSIII and/or color fundus photography during the extension phase (Safety Set-4)

Timepoint	Examination	DFX Cross-over N = 69 n (%)	DFX Granule N = 110 n (%)
Baseline/ Baseline-Ext	2 assessments completed	25 (36.2)	18 (16.4)
	Only one assessment completed	10 (14.5)	13 (11.8)
	Missing assessments	34 (49.3)	79 (71.8)
Week 101	2 assessments completed	16 (23.2)	12 (10.9)
	Only one assessment completed	8 (11.6)	10 (9.1)
	Missing assessments	45 (65.2)	88 (80.0)
Week 153	2 assessments completed	14 (20.3)	12 (10.9)
	Only one assessment completed	5 (7.2)	13 (11.8)
	Missing assessments	50 (72.5)	85 (77.3)
Week 205	2 assessments completed	8 (11.6)	10 (9.1)
	Only one assessment completed	6 (8.7)	6 (5.5)
	Missing assessments	55 (79.7)	94 (85.5)
Week 257	2 assessments completed	8 (11.6)	11 (10.0)
	Only one assessment completed	8 (11.6)	10 (9.1)
	Missing assessments	53 (76.8)	89 (80.9)
Week 309	2 assessments completed	12 (17.4)	14 (12.7)
	Only one assessment completed	3 (4.3)	5 (4.5)
	Missing assessments	54 (78.3)	91 (82.7)
EOT-Ext	2 assessments completed	17 (24.6)	23 (20.9)
	Only one assessment completed	15 (21.7)	14 (12.7)
	Missing assessments	37 (53.6)	73 (66.4)

An examination is considered completed when both eyes are completed with an image quality of High or Borderline

- Lens Opacities Classification System III

SAFETY SET-3

Table 26. LOCSIII shift table during the core phase: Cortical Right Eye (Safety Set-3)

		Baseline	Worst post-baseline value						
			No opacity	C1	C2	C3	C4	C5	Missing
Treatment	n (%)		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All patients (N* = 112)	No opacity	53 (47.3)	34 (64.2)	0	0	0	0	0	19 (35.8)
	C1	0	0	0	0	0	0	0	0
	C2	0	0	0	0	0	0	0	0
	C3	0	0	0	0	0	0	0	0
	C4	0	0	0	0	0	0	0	0
	C5	0	0	0	0	0	0	0	0
	Missing	59 (52.7)	21 (35.6)	0	0	0	0	0	38 (64.4)
	Total	112 (100.0)	55 (49.1)	0	0	0	0	0	57 (50.9)

N* is the number of subjects who have at least one photograph available for evaluation during the study
Abnormal findings assessments can only be collected for images with High or Borderline image quality.
Missing includes the subjects with either image is not available or cannot be graded for that assessment.
Baseline percentage is based on N*. Percentage for worst post-baseline value is based on Baseline n.
The last available value before or on start date of study treatment is taken as 'Baseline' value.
Source: Table 14.3-29.7

Table 27. LOCSIII shift table during the core phase: Cortical Left Eye (Safety Set-3)

		Baseline	Worst post-baseline value						
			No opacity	C1	C2	C3	C4	C5	Missing
Treatment	n (%)		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All patients (N* = 112)	No opacity	52 (46.4)	32 (61.5)	0	1 (1.9)	0	0	0	19 (36.5)
	C1	0	0	0	0	0	0	0	0
	C2	0	0	0	0	0	0	0	0
	C3	0	0	0	0	0	0	0	0
	C4	0	0	0	0	0	0	0	0
	C5	0	0	0	0	0	0	0	0
	Missing	60 (53.6)	21 (35.0)	0	0	0	0	0	39 (65.0)
	Total	112 (100.0)	53 (47.3)	0	1 (0.9)	0	0	0	58 (51.8)

N* is the number of subjects who have at least one photograph available for evaluation during the study
Abnormal findings assessments can only be collected for images with High or Borderline image quality.
Missing includes the subjects with either image is not available or cannot be graded for that assessment.
Baseline percentage is based on N*. Percentage for worst post-baseline value is based on Baseline n.
The last available value before or on start date of study treatment is taken as 'Baseline' value.
Source: Table 14.3-29.7

In Safety Set 3, there were no post-baseline abnormalities or shift from normal at baseline to any grade opacity post-baseline for nuclear color, nuclear opalescence, and posterior subcapsular. One subject with no opacity at baseline had cortical opacity C2 in left eye observed by central reader on lens photograph post-baseline.

• Subject (ICT pre-treated subject in the granules group, 13 years old) had LOCS III grade no opacity in both eyes at Baseline prior to treatment start for Nuclear Color, Nuclear Opalescence, Cortical and Posterior Subcapsular. The LOCS III grade changed to C2 cortical opacity in left eye at Week 25 and EOT-Core as per central reader evaluation. Photographs were not available (due to a loading issue) for the left eye at subsequent assessments at Week 101 and EOT-ext. At both Week 25 and EOT-core visits, the subject had an additional finding of a persistent pupillary membrane (PPM) in both eyes as reported by the central reader. Of note, per the local ophthalmologist's assessment, a clinically insignificant abnormality in both eye's irises was reported from Baseline (thin filamentous PPM) in the slit lamp examination and lens were reported normal. None of these changes were reported as AE.

SAFETY SET-4

In Safety Set 4, no additional subjects had LOCSIII abnormalities.

- Color Fundus Photography

SAFETY SET-3

In Safety Set 3, 2 subjects in the DFX DT group and 1 subject in the DFX granule group reported color fundus photography abnormalities related to retinal pigment epithelium (RPE) changes, at Baseline and/or post-baseline.

Table 28. Color fundus photography abnormalities during the core phase by visit (Safety Set 3)

Visit	Eye side	Findings	DFX DT N*=58 n (%)	DFX Granule N* = 57 n (%)
Baseline	Right eye	No abnormal finding	33 (56.9)	24 (42.1)
		Any Abnormal Finding	1 (1.7)	0
		RPE Changes	1 (1.7)	0
		Atrophy	1 (1.7)	0
		Decreased Pigment	1 (1.7)	0
	Left eye	No abnormal finding	32 (55.2)	24 (42.1)
		Any Abnormal Finding**	2 (3.4)	0
		RPE Changes	1 (1.7)	0
		Atrophy	1 (1.7)	0
		Decreased Pigment	1 (1.7)	0
Week 25	Right eye	No abnormal finding	33 (56.9)	28 (49.1)
		Any Abnormal Finding	1 (1.7)	1 (1.8)

		RPE Changes	1 (1.7)	1 (1.8)
		Decreased Pigment	1 (1.7)	1 (1.8)
	Left eye	No abnormal finding	33 (56.9)	30 (52.6)
		Any Abnormal Finding	1 (1.7)	0
		RPE Changes	1 (1.7)	0
		Atrophy	1 (1.7)	0
		Decreased Pigment	1 (1.7)	0
EOT-Core	Right eye	No abnormal finding	34 (58.6)	30 (52.6)
		Any Abnormal Finding	2 (3.4)	0
		RPE Changes	2 (3.4)	0
		Atrophy	1 (1.7)	0
		Decreased Pigment	1 (1.7)	0
		Increased pigment	1 (1.7)	0
	Left eye	No abnormal finding	35 (60.3)	30 (52.6)
		Any Abnormal Finding	1 (1.7)	0
		RPE Changes	1 (1.7)	0
		Atrophy	1 (1.7)	0
		Decreased Pigment	1 (1.7)	0

Numbers (n) represent counts of subjects.
N* is the number of subjects who have at least one photograph available for evaluation during the study.
Abnormal findings assessments can only be collected for images with High or Borderline image quality.

Details of subjects with any Baseline/ post-baseline abnormalities in Safety Set 3 are presented below:

• Subject (ICT pre-treated subject in the DT group, 9 years old) had RPE changes of atrophy and decreased pigment in both eyes at Baseline and EOT-core visit, and in left eye at Week 25 and Week 101. In right eye, RPE changes (decreased pigment) reported at Week 25 visit, and no abnormality at Week 101.

• Subject (ICT pre-treated subject in the DT group, 15 years old) had no abnormal findings at Baseline but had RPE changes of increased pigment in right eye at EOT-Core visit. The subject reported to have no abnormal findings in subsequent visits of week 101,153 and EOT-ext.

• Subject (ICT pre-treated subject in the granules group, 7 years old) did not have screening visit but had RPE changes of decreased pigment in the right eye on Week 25, 101, 153, 205 and 257. The subject had no abnormal findings at EOT-ext.

SAFETY SET-4

In Safety Set 4, no additional subjects had color fundus photography abnormalities.

Assessor's comment:

Per protocol amendment 6, central collection of some ocular examinations (lens opacities classification system III [LOCS III] and color fundus photography was implemented. Both assessments were performed for all the safety sets but only results from safety set-3 (all subjects who received at least one dose of study drug during the core phase) and safety set-4 were presented above.

Regarding LOCSIII, no post-baseline opacity was reported in safety set-4. One subject in safety set-3 had left cortical opacity with persistent pupillary membrane in both eyes at Week 25 and EOT-Core visit. None of the changes were reported as AEs.

Regarding color fundus photography, no cases were reported in safety set-4. In safety set-3, 2 subjects in the DT group reported such abnormalities at baseline, while 1 subject in the granules group had RPE changes of decreases pigment in the right eye at multiple study time points but presented no abnormal findings at EOT-ext.

Conclusions on ocular examinations

Longer-term treatment with deferasirox appears to be associated with an increase in cases of ocular toxicity, some of which have been suspected to be treatment-related (1 mild AE of retinal pigmentation led to discontinuation of treatment). These events were mainly reported in younger subjects often for prolonged periods, with no systematic discussion of a causal relationship with the administered granules. The MAH is therefore expected to provide a comprehensive analysis of all ocular examinations, detailing changes compared to the results presented for the safety set-3 and discussing the potential causal relationship with the exposition to the granules formulation (**OC**).

Growth velocity and pubertal stage analysis

- Growth velocity

The growth velocity in height evaluates the rate of growth per year and is calculated on the difference with the previous measure if height (in cm) and the time period (in days). Growth velocity was listed at baseline and EOT visit and summarized using descriptive statistics by sex and age group for the entire granule period on the safety set-4.

In the granules group, in the age category 2 to <10 years, the mean EOT-Ext growth velocity was 5.6 cm/year (n = 36) in males and 6.2 cm/year (n = 29) in females. In the age category of 10 to <18 years, the mean of EOT-Ext growth velocity was 4.0 cm/year (n = 4) in males and 1.6 cm/year (n = 7) in females; however, due to small number of subjects in this age category (in both the genders), these results should be interpreted with caution.

In the cross-over group, in the age category 2 to <10 years, the mean EOT-Ext growth velocity was 5.8 cm/year (n = 29) in males and 5.5 cm/year (n = 31) in females. In the age category of 10 to <18 years, the mean of EOT-Ext growth velocity was 1.9 cm/year (n=5) in males and 1.4 cm/year (n = 3) in females; however, due to small number of subjects in this age category (in both the genders) these results should be interpreted with caution.

- Pubertal stage analysis

Delayed puberty in boys is defined as failure to attain Tanner stage 2 for pubic hair and genitals by age 14. Delayed puberty in girls is defined as failure to attain Tanner stage 2 for pubic hair and breast by age 13, or absence of menarche by age 15 or within 5 years of attainment of Tanner stage 2.

In the granules group during the core or extension phase, for both male (pubic hair and genitals staging) (54 subjects) and female subjects (breast development and pubic hair staging) (55 subjects), at Baseline majority of the subjects (42 to 49 subjects) were in Tanner stage 1, the subject at other Tanner stages (Stage 2 to 4) was low (≤ 6 subjects) and none of the subjects were at Tanner stage 5.

Overall, the number of evaluable subjects for Tanner staging decreased over time points in the granules group. Four female subjects in the granules group reached Tanner stage 5 for both breast development and pubic hair stage (1 subject each at Week 153 and Week 205, 2 subjects already at EOT-core). Two of the male subjects reached Tanner stage 5 in the granules group at EOT-ext, 1 subject for penis stage, pubic hair stage and testes stage and 1 subject for penis stage and testes stage.

In the cross-over group during the extension phase, for both male (pubic hair and genitals staging) (35 subjects) and female subjects (breast development and pubic hair staging) (33 subjects), at Baseline-ext a majority (29 to 30 subjects) of the subjects were in Tanner stage 1, the subjects at other Tanner stages (Stage 2 to 4) was low (≤ 4 subjects) and none of the subjects were at Tanner stage 5.

Overall, the number of evaluable subjects for Tanner staging decreased over time points in the cross-over group. One female subject in the cross-over group reached Tanner stage 5 of breast development and pubic hair at Week 205, 1 other subject only for pubic hair at Week 205. Four male subjects (1

subject at Week 153, 1 subject at Week 205 and 2 subjects at EOT-Ext) in the cross-over group reached Tanner stage 5 of pubic hair and genitals stage.

Delayed puberty was reported in 2 male subjects in the granules group during the core or extension phase and 1 male subject in the cross-over group during the extension phase. No AEs related to pubertal development or delayed growth and development were reported in any of these subjects.

• Subject (ICT pre-treated subject in the granules group, aged 10 years at randomization) had delayed puberty (Tanner stage 1 for pubic hair and testes at Week 205; the subject failed to attain Tanner stage 2 (for pubic hair and genitals by age 14). By Week 257 the subject developed to Tanner stage 2 and was at Tanner stage 2 at EOT-Ext visit.

• Subject (ICT pre-treated subject in the granules group, aged 14 years at randomization) had delayed puberty (Tanner Stage 1 for pubic hair and genitals by age 14) at Baseline and EOT-Core visit, no subsequent assessments are available as subject did not continue to extension phase.

• Subject (ICT pre-treated subject in the cross-over group, aged 15 years at randomization) had delayed puberty (Tanner Stage 1 for pubic hair however Tanner stage 2/3 for genitals by age 14) at the Baseline visit, developed to Tanner stage 4 by EOT-core visit, and reached Tanner stage 5 as reported post-baseline at Week 153 visit.

Delayed puberty was reported in 2 female subject in the granules group during the core or extension phase and 3 female subjects in the cross-over group during the extension phase. No AEs related to pubertal development or delayed growth and development were reported in any of these subjects.

• Subject (ICT pre-treated subject in granules group, aged 9 years at randomization) had delayed puberty (Tanner stage 1 for pubic hair and breast development) at Week 205; the subject failed to attain Tanner stage 2 for pubic hair and breast by age 13; Tanner stage 2 was reported at Week 257 and EOT-ext.

• Subject (ICT pre-treated subject in cross-over group, aged 9 years at randomization) had delayed puberty (Tanner stage 1 for breast development and pubic hair stage) at Week 205; the subject failed to attain Tanner stage 2 for pubic hair and breast by age 13).

• Subject ((ICT pre-treated subject in cross-over group, aged 7 years at randomization) had delayed puberty (Tanner stage 1 for breast development and pubic hair stage) at EOT-ext; the subject failed to attain Tanner stage 2 for pubic hair and breast by age 13.

• Subject (ICT pre-treated subject in crossover group, aged 10 years at randomization) had delayed puberty (Tanner stage 1 for breast development and pubic hair) at Week 153; the subject failed to attain Tanner stage 2 for pubic hair and breast by age 13).

Assessor's comment:

Growth velocity: at the previous data cut-off, a higher growth velocity was observed in the DT group compared to the granules group but due to the limited sample size, no new safety concern was raised. As of 26 January 2024, a comparable growth velocity in male and female participants is observed between both groups, regardless of the age category (2 to <10 years and 10 to <18 years) but the sample sizes are even smaller.

Pubertal development: As of last data cut-off, the number of evaluable subjects for Tanner staging was around 100 subjects in each treatment group (DT vs. granules), with approximately 50% of female subjects and 50% of male subjects. Two male subjects (one in each group) presented delayed puberty. As of 26 January 2024, the number of evaluable subjects decreased over time points but delayed puberty was reported 3 male subjects (2 in the granules group and 1 in the crossover group) and 5 females

subjects (2 in the granules group and 3 in the crossover group). Despite the small sample size, yearly monitoring of the impact of deferasirox on development is still deemed necessary as recommended per Exjade SmPC.

Cardiac evaluations

Cardiac evaluations included ECG and echocardiogram. Cardiac evaluations were only required if clinically indicated in the extension phase. No new data has been reported post the previous data cut-off (18-Jan-2021).

- Electrocardiogram (ECG)

In the granule group during the core or extension phase, 1 subject had a clinically significant ECG finding during the study.

• Subject (ICT naive in the granules group) in the core phase had a clinically significant ECG abnormality (electrocardiogram QT prolonged) at Baseline that resolved after 374 days (not suspected to be study drug related by the Investigator). The QTcF at Baseline was 415 ms and 439 ms at EOT-core.

- Cardiac imaging (ECHO)

In the granules group during the core or extension phase, 1 subject had clinically significant Echo/ultrasound finding during the study:

• Subject (ICT pre-treated in the deferasirox granules group) had a clinically significant abnormality and was noted with an AE of left ventricular dilation (mild) during the core phase on Day 332 not suspected to be study drug-related by the Investigator. The event was ongoing at end of study.

One additional subject was noted with a cardiac imaging-related abnormality as described below:

• Subject (ICT naive in deferasirox granules group) had an AE of left ventricular dilation (mild) during the core phase on Day 336 that resolved in 38 days, not suspected to be study drug-related. Overall interpretation was clinically insignificant.

Assessor's comment:

Presented cardiac abnormalities occurred before the previous data cut-off (18-Jan-2021) in 1 subject of the granule group and 2 subjects in the crossover group with left ventricular dilation identified at study baseline. Those events were not suspected to be drug-related.

Audiometric examination

In the granules group during the core or extension phase, for 1 subject post-baseline, clinically significant abnormalities in audiometric examinations was reported:

• Subject (ICT-naïve). The subject had clinically significant abnormality at Week 49, Week 101 and EOT-ext. The subject was noted with an AE of deafness on Day 344 (Week 49) (mild, suspected to study drug) that resolved in 44 days and Day 701 (Week 101) (mild, not suspected to be study drug related) that resolved in 36 days. The subject was also noted with AEs of conductive deafness and mixed deafness on Day 1294 (EOT-ext) (both mild, suspected to be study drug related); both events were ongoing at end of study.

In the cross-over group during the extension phase, post-baseline, clinically significant abnormalities were noted in 7 subjects.

• Subject (ICT-naive subject) with normal assessment at baseline, had a clinically significant abnormality at EOT-Ext visit on Day 2186 (more than 30 days after last study treatment).

• Subject (ICT pre-treated subject) had clinically significant abnormality on Day 1430 (Week 205, last assessment). On the same day, the subject was noted with an AE of neurosensory deafness (mild, suspected to be study drug related); the event was ongoing at end of study. At baseline and other visits during the study, audiometry reported clinically insignificant abnormality.

• Subject (ICT pre-treated) with normal baseline assessment, had clinically significant abnormality on Day 334 (Week 49) and on Day 1401 (EOT-ext). The subject was noted with an AE of conductive deafness (mild, suspected to be study drug related) on Day 334 (Week 49) that resolved in 361 days. The subject was noted with deafness neurosensory on Day 1401 (EOT-ext) (mild, suspected to be study drug related); the event was ongoing at the end of study.

• Subject (ICT naive subject) with normal audiometry at baseline, had clinically significant abnormality on Day 1235 (EOT-ext). On the same day, the subject was noted with an AE of conductive deafness (mild, suspected to be study drug related); the event was ongoing at end of study.

• Subject (ICT naive subject) with normal assessment at baseline, had clinically significant abnormality on Day 1106 (Week 153). On the same day, the subject was noted with an AE of deafness (moderate, not suspected to be study drug related); the event resolved in 289 days and audiometry at final study visit (EOT-ext, Day 1394) reported normal.

• Subject (ICT pre-treated subject) with normal assessment at baseline, had clinically significant abnormality on Day 722 (Week 101). On the same day, the subject was noted with an AE of deafness bilateral (mild, not suspected to be study drug related); the event resolved in 363 days, and audiometry at final study visit (EOT-ext, Day 1310) reported normal.

• Subject (ICT pre-treated subject) with normal assessment at baseline, was noted with a clinically significant abnormality at Week 49, 101 and 153. Thereafter it was judged as normal (Week 205) and insignificant abnormality (Week 257 and EOT- ext). On Day 336 (Week 49) an AE of neurosensory deafness was reported (mild, suspected to be study drug related). The AE was ongoing at end of study.

***Assessor's comment*:**

As of 18 January 2021, 1 subject in the granules group and 6 subjects in the DT group presented clinically significant audition abnormalities. One additional case has been reported since last data cut-off: one patient of the crossover group presented a clinically significant abnormality (not specified) at the end of treatment visit, i.e., more than 30 days after the last dose of study treatment. Previous events were mild to moderate and were suspected to be drug-related. According to the safety profile of deferasirox, decreased hearing is uncommon but yearly examinations are recommended per SmPC.

2.3.3. Discussion on clinical aspects

This P46 procedure is based on the F2022, a phase II study aimed to evaluate the compliance, efficacy and safety of treatment with deferasirox granules compared to orodispersible tablets in paediatric patients with iron overload.

Patients were randomized (ratio 1:1) to the DT or granules arm and received the experimental treatment for 24 weeks. Patients in the DT arm were then given the option to switch to granules for up to 5 years. Assessment of variation II/82/G showed that treatment with deferasirox granules was associated with good treatment compliance, comparable efficacy and safety to the DT formulation (no longer marketed). The Rapporteur recalls that the granules formulation was approved in the EEA in November 2017, however, the MAH confirmed at multiple occasions its unwillingness to commercialize the granules in EU despite the fact that they remain the best treatment option for paediatric and elderly patients with swallowing difficulties.

Longer-term safety follow-up data (up to 6 years) of the deferasirox granules formulation were reported within the final F2022 CSR, from the core and extension phase for subjects randomized to granules (granules group) and the extension phase only for subjects who crossed-over from DT to granules (crossover group).

The safety set-4 (N=179) consisted of all subjects who received at least 1 dose of the granules formulation during the core or extension phase: 110 subjects were initially randomized in the granules arm and 69 subjects were initially randomized to the DT arm and then switched to granules during the extension phase.

Median exposure in the granules group was 25.9 months; 30.0% of the subjects had exposure of > 60 months. The median duration of exposure in the crossover group in the extension phase was 35.1 months, with 15.9% of subjects exposed over 60 months.

There were 63.6% of subjects in the granules group with AEs that required dose adjustments/interruptions in the core and extension phases. In the crossover group, 60.9% of subjects experienced such AEs. In the final CSR, Adverse events leading to dose interruption were not distinguished from those leading to dose adjustment, which did not allow to properly characterize the impact of a long-term treatment with granules on dose modifications (increase, decrease or interruption). In response to RSI, the MAH showed that AEs leading to dose changes were mainly dose interruptions following proteinuria or increased liver transaminases, adverse reactions known to be associated with deferasirox treatment. Dose decreases were motivated by proteinuria or UCPR increased while dose increases were rare and performed to correct serum ferritin levels or iron overload.

In addition, a high frequency of dose changes or interruptions due to dosing errors was observed, despite the existence of a checklist with dosing recommendations/guidelines. As the nature, timing and impact of these dosing errors was not specified, the MAH was requested to review the cases and to discuss the corresponding efficacy and safety outcomes. It is acknowledged that these events represent a short proportion of the full treatment period and the different types of dosing errors have been identified in response to RSI. However, a comprehensive review of the cases (rather than a cross-reference to the individual efficacy and safety listings) is still expected to assess the impact of repeated dosing errors over time on patient outcomes.

An on-treatment death occurred during the extension phase and was not considered related to study treatment despite multiple dosing errors reported for the subject. Based on the detailed narrative provided by the MAH, the impact of repeated dosing errors can be excluded out for this fatal outcome.

The safety profile was overall consistent with previous assessment. In the granules groups, 96.4% of subjects reported AEs: the most commonly (≥ 20%) reported AEs were: upper respiratory tract infection (41.8%), pyrexia (35.5%), urine protein/creatinine ratio increased (35.5%) and alanine aminotransferase increased (23.6%). 66.4% of subjects had AEs suspected to be study drug related: most AEs suspected to be study drug related were reported in < 10% of the subjects.

In the crossover group, 92.8% of subjects reported AEs (regardless of relatedness to study treatment): the most commonly (≥ 20%) reported AEs (by PT) were: urine protein/creatinine ratio increased (52.2%), upper respiratory tract infection (34.8%), pyrexia (21.7%), cough (20.3%) and pharyngitis (20.3%). In the cross-over group, 69.6% of subjects experienced AEs suspected to be study drug related: all AEs suspected to be study drug related were reported in < 10% of the subjects with the exception of urine protein/creatinine ratio increased (47.8%) and ALT increased (13.0%).

In the granules group, 34.5% of subjects reported SAEs: all SAEs were reported in either 1 or 2 subjects with the exception of gastroenteritis, pyrexia and sickle cell anaemia with crisis (4.5% each), acute chest syndrome and cholelithiasis (2.7% each). In the crossover group, 31.9% of subjects reported SAEs: all

SAEs were reported in either 1 or 2 subjects with the exception of gastroenteritis (5.8%) and Fanconi syndrome acquired (4.3%).

The majority of the AESIs were overall manageable with dose interruption/reduction in both, granules and crossover group. Abnormal laboratory values in the notable and extended ranges were low in both granules group and crossover group, including renal lab parameters.

However, longer-term treatment with deferasirox appears to be associated with an increase in cases of ocular toxicity, some of which have been suspected to be treatment-related (1 mild AE of retinal pigmentation led to discontinuation of treatment). They have mainly affected young subjects for prolonged periods. A systematic discussion of a causal relationship with granule treatment has been provided by the MAH but did not allow further characterization of the risk of ocular toxicity since corresponding adverse reactions were infrequent and rarely suspected to be drug-related.

3. Rapporteur's CHMP overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

The timetable is a 30-day response timetable with clock stop.

Other concerns

1. This high frequency of dose changes or interruptions due to dosing errors in both groups should be further discussed by the MAH. A detailed analysis of the potential impact of these frequent dosing errors on the efficacy and safety outcomes of study participants is also expected.
2. Adverse events leading to a dose interruption were not distinguished from those leading to a dose adjustment (presumably dose reduction), which makes it impossible to compare with the corresponding AEs reported at the last cut-off. The MAH is therefore requested to provide a comprehensive analysis distinguishing AEs leading to dose interruption from those leading to dose adjustment (please specify: dose reduction / increase) during the core period compared with those reported during the extension period. A comprehensive discussion on the long-term safety profile of the granules formulation in the light of these results is also expected.
3. One on-treatment death occurred in the crossover group during the extension phase. According to the MAH, this death was not suspected to be drug-related. However, according to the narrative provided, the patient has never been treated at the adequate dose throughout their entire study participation. Possible impact of repeated dosing errors on safety outcomes should be further discussed, based on a comprehensive description of the changes in their condition during treatment, as the diagrams provided in the narrative are not considered sufficiently precise to rule on this aspect.
4. Longer-term treatment with deferasirox appears to be associated with an increase in cases of ocular toxicity, some of which have been suspected to be treatment-related (1 mild AE of retinal pigmentation led to discontinuation of treatment). These events were mainly reported in younger

patients often exposed for prolonged periods, with no systematic discussion of causal relationship with the administered granules. The MAH is therefore expected to provide a comprehensive analysis of all ocular examinations, detailing changes compared to the results presented for the safety set-3 and discussing the potential causal relationship with the exposition to the granules formulation.

MAH responses to Request for supplementary information

Question 1

This high frequency of dose changes or interruptions due to dosing errors in both groups should be further discussed by the MAH. A detailed analysis of the potential impact of these frequent dosing errors on the efficacy and safety outcomes of study participants is also expected.

MAH's response

A detailed summary of dosing errors in subjects who were treated with deferasirox granules during the study (core and/or extension phases) is provided below, together with a clinical assessment of the potential impact of dosing errors on efficacy and safety outcomes. Results are summarized for the granules group during the core and extension phase (granules group N=110; median exposure 25.9 months, with 30% having at least 60 months exposure) and the crossover group during the extension phase (i.e., after they crossed over from DFX DT to granules treatment) (crossover group N=69; median exposure 35.1 months, with 16% having at least 60 months exposure). As detailed below, most dosing errors were brief, overall compliance was high, and even among subjects with longer dosing errors (episodes over 10 consecutive days), there was no evidence of a significant impact on efficacy or safety outcomes.

Dosing error as a reason for dose change was reported on the drug administration record of the Case Report Form (CRF). Dosing error was selected if a subject erroneously took a lower or higher dose than prescribed (underdose or overdose) or missed a dose (interruption). Dosing errors due to receiving the wrong treatment were not reported in the study and will not be discussed further. To perform a detailed analysis of the impact of dosing errors on efficacy or safety, the specific type of dosing error was identified through derivation from subjects' dose administration records. The following categories of dose error were derived for all subjects with complete dosing dates (denoted N* in tables) to summarize frequency of occurrence of these episodes, and their corresponding duration:

• Dose interruption: actual dose of 0

• Underdose: current actual dose (mg/kg/day) was ≤15% than the corresponding planned dose (mg/kg/day)

• Overdose: current actual dose was ≥15% than the corresponding planned dose

• No clinically meaningful change: a minor dose change (actual dose mg/kg/day is within ±15% of the planned dose)

Table 29. Dosing errors of study drug during the entire granule period (Safety Set 4)

	DFX Cross-over N*=61	DFX Granule N*=77
Number of patients with at least one dosing error - M (%)	32 (52.5)	41 (53.2)
Interruptions	32 (52.5)	32 (41.6)
Overdose	2 (3.3)	3 (3.9)
Underdose	7 (11.5)	10 (13.0)
No clinically meaningful change	6 (9.8)	12 (15.6)

Average number of dosing error episodes		
Interruptions		
n	32	32
Mean	10.1	18.0
SD	13.29	20.40
Median	4.0	9.5
Minimum	1	1
Maximum	60	80
Overdose		
n	2	3
Mean	1.5	1.0
SD	0.71	0.00
Median	1.5	1.0
Minimum	1	1
Maximum	2	1
Underdose		
n	7	10
Mean	3.4	1.5
SD	3.26	0.85
Median	2.0	1.0
Minimum	1	1
Maximum	9	3
No clinically meaningful change		
n	6	12
Mean	1.5	1.3
SD	0.84	0.62
Median	1.0	1.0
Minimum	1	1
Maximum	3	3

Dosing error episode categories - n/M (%)		
Interruptions		
1-5	17 (53.1)	13 (40.6)
6-10	6 (18.8)	4 (12.5)
11-15	2 (6.3)	3 (9.4)
>15	7 (21.9)	12 (37.5)
Overdose		
1-5	2 (100)	3 (100)
6-10	0	0
11-15	0	0
>15	0	0
Underdose		
1-5	5 (71.4)	10 (100)
6-10	2 (28.6)	0
11-15	0	0
>15	0	0
No clinically meaningful change		
1-5	6 (100)	12 (100)
6-10	0	0
11-15	0	0
>15	0	0

N* is the number of patients with complete start and end dates. Complete dates are needed to assign overdose, underdose and no clinically meaningful change for the calculation of current actual dose.
- Underdose: if the current actual dose(mg/kg/day) is 15% or lower (<=15%) than the corresponding planned dose(mg/kg/day).
- Overdose: if the current actual dose(mg/kg/day) is 15% or greater (>=15%) than the corresponding planned dose(mg/kg/day).

- No clinically meaningful change: a minor dose change (actual dose mg/kg/day is within +/- 15% of the planned dose).
Percentages for dosing error episode categories are based on number of patients with corresponding dosing error type.

Table 30. Maximum duration of dosing error episodes during the entire granule period (Safety Set 4)

Duration of dosing error interval	DFX Cross-over N*=61	DFX Granule N*=77
Number of patients with at least one dosing error - M (%)	32 (52.5)	41 (53.2)
Interruptions	32 (52.5)	32 (41.6)
Overdose	2 (3.3)	3 (3.9)
Underdose	7 (11.5)	10 (13.0)
No clinically meaningful change	6 (9.8)	12 (15.6)
Interval categories per dosing error episode (days) - n/M (%)		
Interruptions		
<= 3	15 (46.9)	13 (40.6)
>3 - 10	11 (34.4)	11 (34.4)
>10	6 (18.8)	8 (25.0)
Overdose		
<= 3	2 (100)	1 (33.3)
>3 - 10	0	1 (33.3)
>10	0	1 (33.3)
Underdose		
<= 3	5 (71.4)	6 (60.0)
>3 - 10	0	0
>10	2 (28.6)	4 (40.0)
No clinically meaningful change		
<= 3	2 (33.3)	4 (33.3)
>3 - 10	1 (16.7)	1 (8.3)
>10	3 (50.0)	7 (58.3)

N* is the number of patients with complete start and end dates.
- Patient is counted in the category based on their maximum interval per dosing error episode for each dosing error type separately.
Percentages for dosing error episode categories are based on number of patients with corresponding dosing error type.

Dosing errors without a clinically meaningful change in dose

As depicted in Table 29, total of 16% of subjects in the granules group and 10% in the crossover group had dose errors without a clinically meaningful change in dose (all with 1-5 total episodes).

As shown in Tables 29 and 30, these episodes were generally infrequent and of a short duration. Considering the minimal change to planned dose together with the typically short duration and infrequent occurrence, these episodes are not expected to impact the efficacy or safety of deferasirox and are not discussed further.

Dosing errors related to interruptions (missed doses)

Overall, most of the dose errors were interruptions. In Safety Set-4 (N=110 in the granules group, N=69 in the crossover group), 44.5% of subjects in the granules group and 53.6% of subjects in the crossover group had at least one dose interruption, most commonly having 1 to 5 episodes of dose interruptions during their time on study (note that proportions should not be compared between groups, as they were not adjusted for exposure). Over 40% of subjects with dose interruptions had interruptions of 3 days or fewer. Considering that deferasirox is a drug that should be taken daily to treat a chronic condition, it is not unexpected that subjects would occasionally forget to take their daily dose of medication, leading to

brief study drug interruptions that would not be expected to have an overall impact on the efficacy and safety of deferasirox.

Consistent with the overall population (N=179), in the subset of patients with complete date records (N=138), 41.6% of subject in the granules group and 52.5% of subjects in the crossover group had dose interruptions, and over 40% of subjects in both groups had within 1 to 5 episodes of dose interruptions. Twelve subjects (37.5%) in the granules group and 7 subjects (21.9%) in the crossover group had over 15 interruptions; there was no evidence of a significant impact of more frequent dose interruption episodes on subsequent AEs or on serum ferritin.

During the entire granule period, the median duration of exposure to study drug was 25.9 months (approximately 788 days) in the granules group (N=110) and 35.1 months (approximately 1068 days) in the crossover group (N=69). Among subjects with dose interruptions with complete date records, the median total duration of study drug interruptions during the entire granule period was 26.5 days in the granules group and 13.5 days in the crossover group, which represents a small proportion of time (median <3% total duration of dosing error interval relative to the total treatment duration of these subjects).

A majority of patients had short episodes of treatment interruption of up to 3 days (Table 29). Twenty-two subjects had episodes of interruption of >3 to 10 consecutive days, and 14 subjects had longer interruptions of >10 consecutive days. Among subjects with lengthy dose interruptions (>10 days), there was no consistent effect on efficacy, with some subjects experiencing increases in serum ferritin values following treatment interruption episode, and some maintaining stable serum ferritin values or showing overall decreasing trends in serum ferritin values during the study period. With respect to safety, there was no evidence for an association between lengthy dose interruptions and subsequent AEs.

Dosing errors related to underdose

Ten subjects (13%) in the granules group and 7 subjects (12%) in the crossover group had underdoses, and a majority of subjects had 1 to 5 episodes of underdosing (see Table 29 above).

The median total duration of these dosing errors during the entire granule period was 2.5 days in the granules group and 2.0 days in the crossover group, which represents a very small proportion of the total treatment duration of these subjects.

Most episodes were single-day episodes with no impact on efficacy and safety outcomes (Tables 30 and 31). Six subjects had more lengthy episodes of underdosing (more than 10 consecutive days). Among these subjects, no apparent impact of underdosing episodes on serum ferritin trends or safety events was noted. One of these 6 subjects showed a decreasing trend in serum ferritin, reaching below 500 ng/ml by study completion. For the remaining subjects, serum ferritin values were variable across the study period.

Dosing errors related to overdose

There were few cases of overdose: 3 subjects in the granules group and 2 subjects in the crossover group with complete dates (8 subjects when including those with partial dates), all with 1 or 2 episodes of overdose (Tables 29 and 30).

Subject had 2 episodes of overdose, on Day 310 of the extension phase (dose taken was 59.6 mg/kg instead of 28.0 mg/kg, AE of accidental overdose was reported) and Day 1311 (dose taken was 232 mg/kg instead of 28.0 mg/kg). An SAE of overdose was reported on Day 1311. The subject had symptoms of myalgia, odynophagia, diarrhea, vomiting and headache (of note, diarrhea, vomiting, and headache are common adverse reactions even with normal dosage). The subject was hospitalized for observation and monitoring of possible side effects resulting from overdose. The subject was treated

with furosemide and normal saline. On the same day, liver laboratory and renal panel were normal. No liver, ototoxicity, or renal toxicity was reported. On the next day, the subject recovered and was discharged.

Two subjects had an overdose taking approximately double the planned dose of deferasirox granules (52 and 53.3 mg/kg) on single day, with no AEs or lab abnormalities reported after this overdose.

For Subject, an AE of overdose was reported (dose taken was 48.6 mg/kg from Day 88 to Day 96 instead of 24.5 mg/kg). No other AEs or lab abnormalities were reported during or after this overdose.

Four other subjects had single overdose episodes with marginally increased doses: 14 mg/kg instead of 10.5 mg/kg, 21.1 mg/kg instead of 17.5 mg/kg, 29.8 mg/kg instead of 21 mg/kg, 33.5 mg/kg instead of 28 mg/kg. No AEs were associated with these episodes.

Analysis of potential impact of dosing errors on efficacy and safety

Despite dose changes including interruptions and adjustments, the median percentage of planned dose taken was high (>90%). This indicates a minimal impact on overall compliance for majority of subjects.

As noted above, dose interruptions were the most common type of dosing error. At least one episode of missed dose was reported in approximately half of study participants, which is not an unexpected finding during long-term treatment of subjects with transfusional iron overload, as deferasirox must be taken daily over years and occasional missed doses can occur. Brief interruptions are not expected to have an impact on the safety or efficacy of deferasirox.

The small subset of patients with longer or more frequent dose interruptions (>10 consecutive days and/or >10% of overall duration of exposure) was examined for the potential impact on safety and efficacy. Overall, there was no consistent impact of longer dose interruption episodes on the long-term efficacy of deferasirox granules (as indicated by serum ferritin levels). With respect to safety, there was no evidence suggesting an association between longer dose interruptions and the occurrence of subsequent AEs.

Episodes of underdosing were mostly short and were not clearly associated with a lack of efficacy and there was no evidence suggesting an association between underdosing and subsequent AEs.

Minor episodes of overdose were not associated with AEs or lab abnormalities, and for one SAE of overdose, the subject was discharged from the hospital the day after the overdose.

Finally, it is worth noting that overall, there was a consistent trend for decreasing serum ferritin values for the study population across the entire study period, indicative of clinical efficacy.

Assessor's comment:

The MAH provided a review distinguishing the different types of dosing errors that occurred in the granule and crossover groups, focusing on subjects with complete data records (i.e. with start and end dates, 77/110 in the granules group and 61/69 in the crossover group). Dosing error was defined in the CRF as missing a dose (interruption) or taking mistakenly taking a dose at least 15% lower or higher dose than prescribed (under- or overdose). Actual dose within ±15% was considered to be a clinically insignificant change.

Results for the crossover group correspond to the extension phase, while those from the granules group pooled data from the core and extension phases. Separate results between these two treatment periods would have been useful to better appreciate the impact of dosing errors in the granules group.

Dosing errors without a clinically meaningful change in dose

Twelve subjects in the granules group and 6 in the crossover group (15.6% and 9.8%, respectively) had one to five dosing errors with no clinically meaningful change in dose. The duration of the interval between dosing errors was greater than 10 days in more than half of subjects (7 granules and 3 crossover subjects), ≤3 days in a third of them (4 granules and 2 crossover subjects) and between 3 and 10 days in the remainder. The MAH did not presented the efficacy and safety outcomes for these patients, but the impact of these slight dose changes events is expected to be limited since 1 to 5 episodes have been reported for daily granule treatment over a median exposure of 25.9 months in the granules group and 35.1 months in the crossover group.

Missed doses and underdoses

• Most dose errors were interruptions: 44.5% of subjects in the granules group and 52.5% of subjects in the crossover group, driven by subjects with less than 5 episodes (40.6% and 53.1%, respectively) and those with over 15 episodes (37.5% and 21.9%, respectively). In more than 40% of cases in both groups, the interval between dose interruptions was less than 3 days. The interval was between 3 and 10 days in one third of subjects in both groups and >10 days in 20-25% of subjects.

The median total of dose interruptions during the entire granule period was 26.5 days in the granule group and 13.5 days in the crossover group, which is rather negligible considering the median treatment duration in each treatment group. But given physicians' knowledge of Exjade posology as assessed in the survey protocol CICL670A2429 (see ongoing EMEA/H/C/000670/II/0090), the impact of repeated dosing errors should be further investigated for this daily and chronic treatment. But the MAH refers to the individual data listings regarding efficacy response data and adverse events, rather than providing a comprehensive review of the cases. It therefore remains impossible to really appreciate the impact on efficacy and safety outcomes of these errors (**OC**).

• The same conclusion applies to under-dosing, which affected 10 patients in the granule group and 7 in the crossover group. The majority of patients (15 out of 17) experienced 1 to 5 episodes, within an interval of less than 3 days (6 subjects in the granule group and 5 in the crossover group) or more than 10 days (4 subjects in the granule group and 2 in the crossover group). Again, the median duration of underdose (2.5 days in the granules group and 2.0 days in the crossover group) is negligible compared to the total treatment period (**OC**).

Overdoses

Three subjects in the granules group and 2 subjects in the crossover group with complete dates (8 subjects when including those with partial dates) had 1 or 2 episodes of overdose. Only one patient had a SAE of overdose that resolved upon hospitalization and adequate treatment. In the other subjects, overdose was not associated to any AE.

Conclusion

Numerous dose changes or interruptions were reported in the final CSR of Study F2202 in the granule and crossover groups. As the nature, timing and impact of these dosing errors was not specified, the MAH was requested to review the cases and to discuss the corresponding efficacy and safety outcomes. Overall, dosing errors were infrequent and mostly short-term, regardless the type (interruption, increase or decrease). However, a comprehensive review of the cases rather than a cross-reference to the efficacy and safety listings is still required to assess the impact of repeated dosing errors over time on patient outcomes (**OC**).

Question 2

Adverse events leading to a dose interruption were not distinguished from those leading to a dose adjustment (presumably dose reduction), which makes it impossible to compare with the corresponding AEs reported at the last cut-off. The MAH is therefore requested to provide a comprehensive analysis distinguishing AEs leading to dose interruption from those leading to dose adjustment (please specify: dose reduction / increase) during the core period compared with those reported during the extension period. A comprehensive discussion on the long-term safety profile of the granules formulation in the light of these results is also expected.

MAH response

Adverse events leading to dose interruption and/or adjustment were collected under a single codelist on the CRF page, and therefore, interruptions were not distinguished from dose adjustments in the CSR AE summaries. In order to distinguish and report the AEs leading to interruption, dose increase, or dose decrease separately, a mapping of AEs and dose administration records was done programmatically based on concurrence of the AE and drug administration record and further assessed and updated (if needed) based on clinical review.

Safety Set-3 was used for summaries of data from the core study and comprised all subjects who received at least one dose of study drug during the core phase. Safety Set-4 was used for summaries of data from the extension study and comprised all subjects who received at least 1 dose of granule formulation during the core or extension phase.

Adverse events requiring adjustment or study drug interruption

As reported in the CSR, during the core phase of Study F2202, 48.2% of subjects in the granules group and 62.2% of subjects in the DFX DT group had AEs requiring either dose adjustment or study drug interruption; 13.6% and 20.7%, respectively, had severe AEs (per Investigator assessment) requiring dose adjustment or study drug interruption. During the extension phase, 55.8% of subjects in the granules group and 60.9% of subjects in the crossover group had AEs requiring either dose adjustment or study drug interruption; 16.9% and 13.0% of subjects, respectively, had severe AEs requiring either dose adjustment or study drug interruption. The most common reason for dose adjustment or dose interruption during both study phases in both groups was due to AEs of urine protein/creatine ratio increased.

Adverse events leading to specific types of dose adjustment/interruption (increase, decrease, or interruption) are summarized separately for the core and extension phases of Study F2202 below.

Adverse events by specific type of action taken (interruption or dose adjustment)

- *Adverse events requiring dose interruptions in core and extension phases of the study*

Study drug interruptions were the most common type of action taken for AEs. During the core phase, 41.8% of subjects in the granules group and 57.7% of subjects in the DFX DT group had AEs requiring study drug interruptions; 12.7% of subjects in the granules group and 19.8% of subjects in the DFX DT group had severe AEs requiring dose interruption, with the majority of these AEs being lab value abnormalities. The most frequent AEs (>5% in either group) requiring dose interruptions were AEs of bilirubin conjugated increased, urine protein/creatinine ratio increased, pyrexia, alanine aminotransferase increased, aspartate aminotransferase increased, and proteinuria. The most common severe AE requiring dose interruption was alanine aminotransferase increased (5.5% in the granules group, 6.3% in the DFX DT group). Around a quarter of patients in the granules group and a third in the DFX DT group had AEs requiring dose interruption that were suspected by the Investigator to be related to study treatment, and this was mainly driven by AEs of bilirubin conjugated increased, urine

protein/creatinine ratio increased, alanine aminotransferase increased, and aspartate aminotransferase increased.

During the extension phase, approximately half of all subjects had AEs requiring study drug interruption; 16.9% of patients in the granules group and 11.6% of patients in the crossover group had severe AEs requiring dose interruptions. Consistent with the core phase, the most common AEs were lab value abnormalities, including events of urine protein/creatinine ratio increased, alanine aminotransferase increased, and proteinuria. Severe AEs requiring study drug interruption in the extension phase happened in 2 or fewer subjects with the exception of urine protein/creatinine increased in the granules group (5 subjects, 6.5%). A little over a third of subjects in both treatment groups had AEs requiring study drug interruption that were suspected by the Investigator to be related to study drug, the most common of which were AEs of urine protein/creatinine ratio increased.

Overall, the patterns of AEs requiring study drug interruption were similar in the extension phase to what was observed in the core phase of Study F2202. Common AEs requiring dose interruptions were urine protein/creatinine ratio increased and increases in liver transaminases. Both proteinuria and increased liver transaminases are known potential adverse reactions to deferasirox.

- *Adverse events requiring dose decrease in core and extension phases of the study*

During the core phase of Study F2202, 12.7% of subjects in the granules group and 13.5% of subjects in the DFX DT group had AEs requiring a dose decrease, none of which were severe. The most common AEs were urine protein/creatinine ratio increased and proteinuria, most of which were suspected by the Investigator to be related to study drug.

During the extension phase, a little under a third of subjects had AEs leading to dose decrease in both groups (28.6% in the granules group and 31.9% in the crossover group), and only 1 subject in each treatment group had severe AEs leading to dose reduction (events of urine protein/creatinine ratio increased in 1 subject in the granules group and alanine aminotransferase increased and aspartate aminotransferase increased in 1 subject in the crossover group). Consistent with the core phase, dose reductions were largely driven by events of urine protein/creatinine ratio increased and proteinuria, most of which were suspected by the Investigator to be related to study drug.

These findings for dose reductions are consistent with the known safety profile of deferasirox, as proteinuria is a known ADR for which dose reduction may be considered.

- *Adverse events requiring dose increase in core and extension phases of the study*

Three subjects had AEs in the core phase that led to dose increase. These were iron overload (1 subject) and serum ferritin increased (2 subjects), both of which would be expected to lead to an increase in dose in the target population of patients with transfusion-dependent anemia.

None of these events was severe, and no other AEs were reported concurrently with iron overload or serum ferritin increased.

No subjects had AEs leading to dose increase in the extension.

Conclusions

Overall, an analysis of AEs requiring dose increase, decrease, or interruption during the core phase and during long-term treatment with granules formulation in the extension phase did not reveal any new signals with respect to the types of AEs that lead to a dose increase, decrease, or interruption following treatment with deferasirox granules. AEs requiring dose increases were those expected for subjects receiving frequent transfusions. Common AEs requiring dose decreases or interruptions were consistent

with the known safety profile of deferasirox and with the safety profile of the target population (paediatric patients with transfusion-dependent anaemia).

***Assessor's comment*:**

The MAH was requested to provide a review distinguishing AEs leading to a dose interruption than those leading to dose increase or decrease during the core phase compared to the extension phase in order to better characterize the long-term safety profile of the granule formulation.

AEs leading to dose interruption

During the core phase, 41.8% of subjects in the granules group and 57.7% of subjects in the DFX DT group had AEs requiring study drug interruptions; driven by lab values abnormalities (Bilirubin conjugated increased, AST/ALT increase, UPCR increase) and pyrexia. Severe AEs requiring dose interruption (mostly lab value abnormalities) occurred in 12.7% of subjects in the granules group and 19.8% of subjects in the DFX DT group. AEs suspected to be related to study treatment were also driven by above mentioned lab value abnormalities.

The same trend was observed during the extension phase with approximately half of all subjects had AEs requiring study drug interruption. The most common AEs were events of UPCR increased, AST increased, and proteinuria. Severe AEs were reported in 16.9% of patients of the granules group and 11.6% of patients of the crossover group, also driven by proteinuria and increased liver transaminases.

Overall, AEs leading to dose interruptions were mainly caused by proteinuria and increased liver transaminases, adverse reactions known to be associated to deferasirox treatment.

AEs leading to dose decrease

During the core phase of Study F2202, 12.7% of subjects in the granules group and 13.5% of subjects in the DFX DT group had non-severe AEs requiring a dose decrease. The most common AEs were UPCR increased and proteinuria and mainly suspected to be study drug.

During the extension phase, dose reductions occurred in 28.6% of subjects of the granules group and in 31.9% of the crossover group, with 1 subject in each group with a severe AE (UPCR increased for the subject in the granule group and AST increased for the one in the crossover group). Consistently with the core phase, dose reductions were driven by UPCR increased and proteinuria, most of which were suspected to be drug-related.

AEs leading to dose increase

Three subjects had AEs leading to dose increase during the core phase due to serum ferritin increased (2 subjects in the DT group) or iron overload (1 subject in the granules group) that resolved upon treatment. No AEs leading to dose increase occurred in the extension phase.

Conclusion

As requested, the MAH thoroughly discussed the AEs leading to dose interruption or dose adjustments. Those events were driven by proteinuria and increase in liver transaminases, which is consistent with the known safety profile of deferasirox. Issue solved.

Question 3

One on-treatment death occurred in the crossover group during the extension phase. According to the MAH, this death was not suspected to be drug-related. However, according to the narrative provided, the patient has never been treated at the adequate dose throughout their entire study participation. Possible impact of repeated dosing errors on safety outcomes should be further discussed, based on a

comprehensive description of the changes in their condition during treatment, as the diagrams provided in the narrative are not considered sufficiently precise to rule on this aspect.

MAH response

A detailed narrative of this patient's condition throughout the study is provided below.

Subject was a 14-year-old Caucasian male patient with beta-thalassemia major. The subject had a medical history of splenectomy, osteopenia, and thrombocytosis and was overweight. The subject was ICT pre-treated and was in the DFX DT group during the core phase of the study, crossing over to the DFX granule group during the extension phase. The subject died of sudden death. The death was not suspected by the Investigator to be related to the study medication. No autopsy was performed.

Chelation therapy prior to study entry included DFX. Relevant medical history included splenectomy. Active medical conditions included osteopenia and thrombocytosis. Relevant concomitant medications included folic acid and -D-calsor (calcium carbonate, cholecalciferol).

At the Screening Visit 1 on Day −20, serum ferritin was 1132 ng/mL (normal range: 10 to 105 ng/mL) and at the Screening Visit 2 on Day −13, serum ferritin was 1034 ng/mL. On the next day, an audiometric test showed a clinically insignificant abnormality.

The subject was randomized and received the first dose of the study medication (DFX DT) on Day 1 at a dose of 25 mg/kg/day (2000 mg/day. The DFX DT dose was reduced to 20 mg/kg/day on Day 72, then to 15 mg/kg/day on Day 183, and to 10 mg/kg/day on Day 282 (this dose was maintained until end of core study) as per protocol (due to decreasing trend in serum ferritin values). During the 48-week core phase, the subject reported a total of 9 days of missed doses due to dosing error: 7 single-day interruptions, which occurred on Days 31, 174, 233, 264, 268, 312, and 321, and 1 two-day interruption due to an AE of pyrexia, which was mild, not suspected to be treatment-related, and resolved in 5 days. Serum ferritin ranged between 654 and 1485 ng/mL during the core phase of the study.

Additional treatment-emergent AEs that occurred during the core phase of the study that were not serious, not suspected by Investigator to be treatment-related, and did not result in dose adjustment/dose interruption included:

• *Peripheral swelling*: Subject experienced left foot swelling on Day 129 that resolved in 2 weeks

• *Gastroenteritis, viral*: Subject had mild viral gastroenteritis during the core study

• *Dry eye*: Subject experienced dry eye during the core study

• *Skin laceration*: Subject had a cut in his right hand that resolved the same day

• *Limb injury*: Subject sustained a wound on right thumb that resolved the same day

The subject completed the core phase of the study as per protocol and received the last dose of study medication (DFX DT 10 mg/kg/day) on Day 337. The serum ferritin level at end of treatment (EOT) of the core study was 1485 ng/mL.

The subject entered the optional extension phase and started to receive DFX granules at 7 mg/kg/day (540 mg/day) on Day 338. The subject had the following dose increases thereafter:

• Day 424: dose increased to 10.5 mg/kg/day (900 mg/day) as per protocol.

• Day 535: dose increased to 17.5 mg/kg/day (1440 mg/day) as per protocol.

• Day 704: dose increased to 21 mg/kg/day (1890 mg/day) as per protocol.

• Day 816: dose increased to 24.5 mg/kg/day (2250 mg/day) as per protocol.

• Day 934: dose increased to 28 mg/kg/day (2880 mg/day) as per protocol.

During the extension phase (total of 1366 days), the subject had 52 episodes of dosing errors, a majority of which were 1- or 2-day study drug interruptions (Table 2-2).

On Day 1066, glucose was detected in the subject's urine. The dipstick urine glucose test was 3+ or 1 g/dL, and the dipstick urine ketone test was 3+. On Day 1071, the subject experienced somnolence and fatigue and was hospitalized. The subject was diagnosed with diabetes mellitus (moderate) and diabetic ketoacidosis (severe), with blood glucose at 700 g/dL (normal range not reported). The study treatment was interrupted from Day 1071 to Day 1078. The subject was treated with regular insulin, insulin degludec, insulin glargine, and insulin glulisine. Diabetic ketoacidosis resolved on Day 1079, and the subject was discharged from the hospital. The Investigator did not suspect a relationship between diabetic ketoacidosis and the study medication. The study medication was restarted on Day 1079 at 28 mg/kg/day (actual dose received was 2520 mg instead of 2880 mg). On Day 1080, the dose of the study medication was increased to 28 mg/kg/day (2880 mg/day). The presence of glucose in his urine resolved on Day 1094 (laboratory results not reported).

On Day 1430, the subject's audiometric test revealed a clinically significant abnormality, and the subject was diagnosed with deafness neurosensory (mild). The study medication dose was reduced to 21 mg/kg/day on Day 1437 due to neurosensory deafness and was maintained at 21 mg/kg/day for the remainder of the subject's participation in the study. No concomitant treatment was reported. The Investigator suspected a relationship between deafness neurosensory and the study medication.

On Day 1497, the subject had headache, cough, shortness of breath, and fever and was hospitalized. PCR was positive for COVID-19 (moderate severity, SAE). SPO_2 was 87% and blood glucose was around 400-500 mg/dL. The study treatment was interrupted from Day 1500 until Day 1509, and the subject received oxygen therapy and insulin along with dexamethasone, enoxaparin sodium, levofloxacin, omeprazole, acetylsalicylic acid, biperiden, ceftriaxone, systemic corticosteroids and paracetamol. On Day 1518, the subject recovered and was discharged from the hospital.

On Day 1704, the subject had a blood transfusion at a local hospital. The subject was conscious and cooperative after leaving the hospital. On the same day, the subject had fatigue, and the subject's glucose test result was around 300 mg/dl. Reportedly, the subject went to sleep afterwards and was awakened later to receive an insulin injection. The subject was given a Lantus (insulin glargine) injection, and the subject went back to sleep. Thirty minutes later, the subject's mother noticed that the subject was snoring and gasping for air. The subject was transferred to the hospital where the subject was found to be unconscious. Cardiopulmonary resuscitation was performed. However, the subject did not respond. The subject died, and no autopsy was performed. Reportedly, there was no direct etiologic factor causing sudden death, and it was not confirmed whether hypoglycemia or hyperglycemia might have been a factor leading to the death.

Summary of all non-serious AEs during the extension phase

In addition to the serious AEs summarized above for the extension phase of the study, the following non-serious AEs occurred:

• Upper respiratory tract infection (3 events, on Day 437, Day 1162, Day 1282, all of which resolved and none of which were suspected of being related to study drug).

• Vitamin D deficiency (Hypovitaminosis D): Moderate severity vitamin D deficiency was reported on Day 416 and was ongoing at the time of subject's death. It was not suspected of being related to study drug.

• Diarrhea: 2 events, on Day 613 and Day 643, both events were mild, suspected by Investigator to be treatment-related, and resolved while the study treatment continued.

• Vomiting: Subject had vomiting on Day 645 that was mild and resolved the same day. It was suspected by the Investigator of being related to study drug. No action was taken.

• Glucose urine present: Glucose in urine was reported for the subject on Day 1066. It was mild and not suspected of being related to study drug. No action was taken, and the event resolved in one month.

Treatment compliance and serum ferritin levels throughout study

Study drug was to be taken daily, with dose adjustments permitted as described in protocol. Overall, the subject had a high compliance of >90% across the entirety of the study, with 60 episodes in total of dosing errors (Table 31). A majority of the dosing errors were individual events of missed doses for 1-2 days (103 days (6%) of dosing interruptions out of 1703 days on study), with drug intake resumed on the subsequent day. Short, 1- or 2-day intervals of missed doses are not unexpected for a treatment that must be taken daily over years to manage a chronic condition. Longer periods of missed doses typically corresponded with the timing of AEs (e.g., 8 missed doses when the subject was hospitalized for diabetes, 10 missed doses when subject was hospitalized with COVID-19).

Overall, the subject maintained serum ferritin levels close to the target range (500 to 1000 ng/mL) for a patient with transfusion-dependent beta-thalassemia major who is being treated with deferasirox ICT. Serum ferritin levels ranged between 654 and 1485 ng/mL during the core study and between 887 and 1866 ng/mL during the extension phase. Brief interruptions in study drug administration did not lead to significant increases in serum ferritin levels (see table below). Longer dose interruptions typically coincided with AEs (upper respiratory tract infection, diabetic ketoacidosis, COVID-19). The last measured serum ferritin level prior to the subject's death was 1190 ng/mL, and the most recent dose level was 21 mg/kg/day, which is considered an adequate dose per protocol for the subjects' condition and serum ferritin levels. The most recent missed dose was 30 days prior to death (2 missed doses due to dosing error on Days 1673 and 1674).

Conclusion

Throughout the study, the subject was largely compliant with the study drug (>90%), mainly missing 1-2 days of doses before resuming daily dosing. These missed doses did not lead to significant increases in serum ferritin levels. A majority of the AEs that occurred during the core and the extension phase were not suspected to be related to the study treatment. The suspected treatment-related AEs were mild and included deafness neurosensory, diarrhea, and vomiting which are listed in the CDS as ADRs reported in clinical trials. The safety findings are in line with the safety profile of deferasirox, and based on available data, there is no evidence of a causal relationship between these dosing errors and the subject's safety outcomes.

***Assessor's comment*:**

As requested, the MAH provided the detailed narrative of the patient in crossover the group whose death was not suspected to be related to study treatment, despite the fact that this patient was not always treated at the adequate dose throughout their study participation.

The patient initially received DFX DT at a dose of 25 mg/kg/day that was reduced to 15 mg/kg/day and then 10 mg/kg/day due to decreased serum ferritin levels, as per protocol. Seven single-day dose interruptions and 1 two-day interruption due to a mild AE of Pyrexia were reported during the core phase. The impact on efficacy and safety outcomes was limited (no significant fluctuations of serum ferritin levels nor major treatment-emergent AEs)

Fifty-two dosing errors were reported during the extension phase (1366 days). On Day 1066, the subject was diagnosed with diabetes mellitus and diabetic ketoacidosis (not suspected to be related

to study treatment), which led to an 8-day dose interruption. Treatment was restarted at 28 mg/kg/day. Glycosuria resolved later (Day 1094).

On Day 1930, the dose was reduced to 21 mg/kg/day following a mild deafness neurosensory suspected to be drug-related. Two months after (Day 1497), the patient contracted COVID-19 and recovered upon treatment and hospitalization on Day 1518.

On Dy 1704, the subject received a blood transfusion at a local hospital and returned home where he received an insulin injection. He was found snoring and gasping for air later that night and did not respond to cardiopulmonary resuscitation.

Conclusion

Based on the detailed narrative provided by the MAH and the AEs reported, this on-treatment death dose not appeared to be drug-related nor caused by repeated dosing errors. Issue solved.

Question 4

Longer-term treatment with deferasirox appears to be associated with an increase in cases of ocular toxicity, some of which have been suspected to be treatment-related (1 mild AE of retinal pigmentation led to discontinuation of treatment). These events were mainly reported in younger patients often exposed for prolonged periods, with no systematic discussion of causal relationship with the administered granules. The MAH is therefore expected to provide a comprehensive analysis of all ocular examinations, detailing changes compared to the results presented for the safety set-3 and discussing the potential causal relationship with the exposition to the granules formulation.

MAH response

The overall incidence of ocular findings in Study F2202 was low considering the long study duration of up to 6 years (median of 2 to 3 patient-years of exposure in the crossover and granules groups, respectively). A detailed discussion of ocular findings is provided below.

Ocular examinations were performed as part of the standard safety assessments for Study F2202. Subjects were to undergo ophthalmologic examinations during the core phase at Screening, Week 25, Week 48 and at unscheduled visits if needed. During the optional extension phase, assessments were to be done annually as per Exjade Prescribing Information. Exams included distance visual acuity test, applanation tonometry, slit lamp exam and lens photography, fundus exam, and wide-angle fundus photography of the retina and optic nerve. For the Final Analysis of Study F2202, analyses of ocular safety were based on Safety Set-4 (N=179), which consisted of all subjects who received at least 1 dose of granule formulation during the core or extension phase.

The focus of the examinations was to evaluate ocular AESIs previously described with deferasirox and other iron chelators (lens opacity, retinal changes, and optic neuritis) and changes/abnormalities in the ophthalmological exams during long-term treatment with deferasirox granules. The comprehensive analysis of the findings and any potential causal relationship with deferasirox is presented below.

<u>Summary of ophthalmological examinations</u>

Visual acuity

Eleven subjects (6.1%) across both groups had a clinically relevant decrease in visual acuity (logMAR score increase of ≥0.2) at any visit post-baseline: 8 subjects (7.3%) in the granules group and 3 subjects (4.3%) in the crossover group.

Of these 11 subjects, 4 subjects (all in the granules group) had abnormalities deemed clinically significant by the Investigator:

• A 6-year-old had an event of amblyopia of the right eye that was reported in the medical history and was ongoing at Screening and Week 25 visits.

• A 9-year-old had an AE of myopia (moderate severity) that started on Day 717 and was ongoing at end of study.

• A 9-year-old had an AE of myopia (mild severity) that started on Day 199 and was ongoing at end of study. Visual acuity was normal after correction with glasses.

• A 7-year-old had an AE of bilateral visual acuity reduced (moderate severity) that started on Day 329 and was ongoing at end of study.

All these abnormalities are related to refraction error and were not suspected by the Investigator to be related to the study drug.

The remaining 7 cases of decreases in visual acuity were considered clinically insignificant by the Investigator, and no associated AEs were reported. Among these 7 subjects, 5 had their logMAR score either return to the baseline value or improve at subsequent visits (with or without correction).

Intraocular pressure (IOP)

• Most subjects in the granules group (80.0%) and the crossover group (76.8%) had normal IOP values post-baseline (i.e., values of >5 to ≤21 mmHg). Increases from baseline of between ≥5 mmHg and <10 mmHg at any post-baseline assessment were reported in 20.0% of subjects in the granules group during the core or extension phase and 15.9% of subjects in the crossover group in the extension phase. No subjects had a ≥10 mmHg increase from baseline. A decrease of >5 mmHg and <10 mmHg from Baseline at any post-baseline assessment was reported in 21 subjects (19.1%) in the granules group and 8 subjects (11.6%) in the crossover group. A decrease of >10 mmHg from Baseline was reported in 2 subjects (1.8%) in the granules group and 1 subject (1.4%) in the crossover group. Overall, the analysis of IOP data showed variability of IOP values at yearly assessments, remaining within normal range, and no consistent increases in IOP were observed in subjects treated with deferasirox.

• Six subjects (5.5%) in the granules group had at least one post-baseline IOP absolute value of >21 to ≤30 mmHg, and in all cases except 1, the Investigator considered this clinically insignificant. For the remaining case, 1 subject had a mild AE of ocular hypertension (IOP 24 mmHg) that was not suspected by the Investigator to be related to study drug. No action was taken, and the event resolved in 408 days.

• Two subjects (2.9%) in the crossover group had at least one post-baseline absolute value of >21 to ≤30 mmHg, and in one case, this was considered clinically significant: 1 subject had a mild AE of ocular hypertension on Day 1827 (IOP 25 mmHg) that was suspected by the Investigator to be related to study drug. Concomitant medication was given, and the event resolved in 33 days.

Slit lamp examination

During the extension phase, a majority of subjects did not have abnormalities in slit lamp examination that were deemed clinically significant by the Investigator. Clinically significant abnormalities on slit lamp exam per Investigator assessment were reported in 3 subjects (two in the granule group, and one in the cross-over group) and included the following AEs: epiblepharon, punctuate keratitis, conjunctivitis, chalazion. These AEs were not suspected to be treatment-related and resolved with no action taken with deferasirox treatment.

Few subjects had insignificant lens abnormalities observed at any post-baseline visit. For one subject, an AE of lenticular pigmentation (mild, not suspected to be study drug-related by the Investigator) was reported on Day 29 that was ongoing. No AEs of lens opacity or cataract were reported.

Fundus oculi exam

During the extension phase, all subjects except 1 (described below) did not have clinically significant fundus oculi abnormalities in the extension phase:

• A 4-year-old subject in the granules group who had an AE of lenticular pigmentation from Day 29 onwards (described above), developed further AEs of visual acuity tests abnormal and retinal pigmentation from Day 394 (EOT-extension) onwards. Both AEs were suspected to be study drug-related by the Investigator. The AE of retinal pigmentation led to discontinuation from the study. Of note, the event was mild and reversable upon treatment discontinuation.

• For a few subjects, insignificant findings were reported at some post-baseline assessments, not showing any specific trend to suspect a role of deferasirox.

LOCS III and color fundus photography

The numbers of subjects with completed LOCSIII or color fundus photography assessments by central reader were low, as these assessments were implemented at a later stage of the study following Protocol Amendment 6. These outcomes were analyzed for Safety Set-3 (all subjects who received at least one dose of study drug during the core phase) because of the late implementation of the assessments following the protocol amendment.

• LOCS III: There were no post-baseline abnormalities or shifts from normal at baseline to any grade opacity post-baseline for nuclear color, nuclear opalescence, and posterior subcapsular. One subject (granules group) had a shift from no opacity to C2 cortical opacity on one eye post-baseline per central reader assessment. Subsequent photographs to assess this finding further were not available. Of note, the local ophthalmologist did not report lens opacity for this subject.

• Color fundus photography: Three subjects (2 subjects in the DFX DT group and 1 subject in the granules group) had findings of retinal pigment epithelium changes on the color fundus photography examinations.

Summary of ocular AESIs

Among subjects treated with deferasirox granules (Safety Set-4, N=179), only 2 subjects (1.8%) in the granules treatment group had ocular AESIs, as described below. No ocular AESIs were reported for the crossover group.

• One subject (4-years-old) had events of lenticular pigmentation (core phase), retinal pigmentation (extension phase) and visual acuity tests abnormal (extension phase). The events of retinal pigmentation and visual acuity tests abnormal were suspected to be study drug-related by the Investigator, and the event of retinal pigmentation led to discontinuation of the study drug. All 3 events were ongoing at the time of discontinuation. All events were of mild severity. None of the events were serious or required additional therapy and the event of retinal pigmentation was reversable upon treatment discontinuation.

• One subject (7-years-old) had visual acuity reduced (core phase), which was ongoing at EOT. The event was not suspected by the Investigator to be related to study drug. The event was moderate in severity, non-serious, and did not require additional therapy.

No cases of optic neuritis were reported.

Causality assessment and overall conclusions

In the Final CSR for Study F2202, 179 pediatric subjects in Safety Set-4 provided ocular safety data following up to a maximum of 6 years of exposure to deferasirox granules.

There were 4 subjects in Safety Set-4 (N=179) with decreases in visual acuity considered clinically significant by the Investigator, none of which were suspected by the Investigator to be related to study drug and which were related to refraction error (e.g. myopia), which is a common finding in the pediatric population. Among subjects with clinically insignificant decreases in visual acuity, most subjects experienced an improvement or return to normal in visual acuity (with or without correction with glasses) during the study. Overall, there were no clear patterns for changes in visual acuity among subjects exposed to deferasirox granules in Study F2202.

A majority of subjects (~80%) had normal IOP during the study, and no subjects had a ≥10 mmHg increase from baseline. There were a few cases of slightly increased IOP value (> 21 mmHg) at single timepoints, which were considered clinically insignificant with the exception of 2 cases when AEs of mild ocular hypertension were reported by Investigator. Both resolved with no action taken to deferasirox treatment. Overall, the analysis of IOP data showed variability of IOP values at yearly assessments, mostly remaining within normal range, and no consistent increases in IOP values were observed in subjects treated with deferasirox that could suggest a detrimental effect of deferasirox.

A small proportion of subjects had abnormalities in slit lamp examinations, with no clear change pattern from baseline. A few subjects had insignificant lens abnormalities observed at any post-baseline visit by local ophthalmologist. However, no AEs of lens opacity/cataract were reported.

Thus, these data are not indicative of a meaningful impact of deferasirox treatment on slit lamp exam outcomes.

Only 1 subject in the extension phase had an abnormality on fundus exam (mild retinal pigmentation) that was considered clinically significant and treatment-related by the Investigator, and a few subjects had insignificant findings at single visits not showing any clear pattern to suspect a role of deferasirox.

The numbers of subjects with completed LOCSIII or color fundus photography assessments by central reader were low, as these assessments were implemented at a later stage of the study following Protocol Amendment 6. Among the subjects for whom LOCS III data were available, only 1 case of a shift from no opacity to C2 cortical opacity in one eye at one post-baseline assessment was reported by the central reader. The data available for color fundus photography did not reveal any safety concerns, as few subjects had findings related to retinal pigment epithelium changes, and no clear pattern was seen.

Few ocular AESIs were reported in the study during the entire granule period, suggesting no increased ocular toxicity with long-term treatment. During the entire granules treatment period, two subjects (1.8%) had ocular AESIs: lenticular pigmentation, retinal pigmentation, and visual acuity tests abnormal in one subject and visual acuity reduced in a second subject. The event of mild retinal pigmentation led to discontinuation of the study drug. Considering Safety Set-3, additional events reported during the core phase in the DFX DT group included an AE of retinal tear that was not suspected by the Investigator to be treatment-related and resolved. Thus, overall, in the study, only 3 subjects (1.4%) had ocular AESIs. No AEs of optic neuritis, lens opacity or cataracts were reported.

The cumulative ocular data from Study F2202 do not reveal any new safety signals for ocular toxicity in the paediatric population. Overall, results from in-depth analysis of the ocular safety data encompassing ocular examinations, assessment of AEs, AESIs, and long-term data, are consistent with the known ocular safety profile of deferasirox.

Assessor's comment:

The MAH was requested to discuss the cases of ocular toxicity reported during the core phase compared to the extension phase as some adverse reactions have been reported in younger subjects. A discussion about the potential causal relationship with granule treatment was expected.

The MAH provided a summary of the ocular AEs. As described in the final CSR, no major changes were reported for lens opacities classification III (LOCS III) and color fundus photography. In addition, AEs related to visual acuity and sit lamp examination were not suspected to be drug-related.

Based on this updated review, no causal relationship was established between granules treatment and clinically significant abnormalities reported for intraocular pressure (IOP) values and fundus oculi exams, except for 1 patient with retinal pigmentation that led to treatment discontinuation.

Emphasis was made in the question about the young age of the subjects with ocular toxicity (all ≥9 years old) but given the rarity of these adverse reactions, no pattern can be drawn at this stage. Overall, this cumulative overview of ocular AEs did not reveal any new safety signals for ocular toxicity but further supports the need for characterization of the important potential risk 'Lens opacities, retinal changes and optic neuritis' listed in the last approved version of the RMP. Issue solved.

5. 2nd Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of a follow-up procedure (P46/01022):

The timetable is a 30-day response timetable with clock stop.

Other concerns

1. A detailed and comprehensive review of the cases of dosing errors rather than a cross-reference to the efficacy and safety listings is still required to assess the impact of repeated dosing errors over time on patient outcomes.

MAH responses to Request for supplementary information

Question 1

A detailed and comprehensive review of the cases of dosing errors rather than a cross-reference to the efficacy and safety listings is still required to assess the impact of repeated dosing errors over time on patient outcomes.

MAH response

A detailed review of the cases of dosing errors in patients treated with deferasirox granule formulations during the core and/or extension phase was completed and is presented in e-narratives in [Appendix 1] to this document. Patient e-narratives are provided for all patients who had at least one dosing error (missed dose, underdose, overdose). Dosing error as a reason for dose change was reported on the drug administration record of the Case Report Form (CRF). Dosing error was selected if a subject erroneously took a lower or higher dose than prescribed (underdose or overdose) or missed a dose (interruption). Few patients with exclusively minor dosing errors (within 15% of the planned dose), defined as 'no clinically meaningful change in dose', were not included in this detailed review.
Of note, dose adjustments were permitted in the study for reasons outlined in detail in the protocol (e.g., based on serum ferritin levels, changes in body weight, or changes in lab values), and thus, a certain amount of variability in the doses that patients receive is expected.
Dose interruptions were the most common error, with about half the participants reporting at least one missed dose, which is not unexpected during long-term treatment of a chronic condition. Brief interruptions did not affect the safety or efficacy of deferasirox. A small subset of patients had longer or more frequent dose interruptions (>10 consecutive days and/or >10% of exposure duration), episodes of underdosing or overdose. Minor episodes of overdose were not associated with AEs or lab abnormalities, and for one SAE of overdose, the subject was discharged from the hospital the day after the overdose.

<u>Conclusion</u>
Overall, for majority of patients, dosing errors did not appear to significantly impact the long-term efficacy or safety of deferasirox granules (indicated by serum ferritin trends and AE data).

Despite dose changes, interruptions, and adjustments, over 90% of the planned dose was taken, showing minimal impact on overall compliance for most subjects.

Assessor's comment:

The MAH provided a very succinct description of dosing errors, not addressing CHMP's request for a clear and comprehensive safety and efficacy review of such errors on patients' outcomes.

The furniture of individual narratives is not what was requested and is not acceptable.

The MAH should put all efforts in order to better address CHMP requests and provide a clear and comprehensive review of dosing errors' cases rather than cross-references or line listings of cases. A comprehensive analysis of the impact of dosing errors over time on patient outcomes is still awaited.

6. 3rd Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of a follow-up procedure (P46/01022):

The timetable is a 30-days response timetable.

Other concerns

1. The MAH should provide a clear and comprehensive review of dosing errors' cases rather than cross-references or line listings of cases as twice provided. A comprehensive analysis of the impact of dosing errors over time on patients' outcomes is still awaited.

MAH responses to Request for supplementary information

Question 1

The MAH should provide a clear and comprehensive review of dosing errors' cases rather than cross-references or line listings of cases as twice provided. A comprehensive analysis of the impact of dosing errors over time on patients' outcomes is still awaited.

MAH response

A comprehensive clinical review of dosing errors based on case narratives and impact analysis on patients' outcomes are presented below, with a comprehensive analysis of the impact of dosing errors in the discussion section below. The total number of cases reviewed with any dosing error is 106. For cases of missed doses/underdosing, a review of the AE data did not suggest any impact on safety outcomes from these dosing errors, therefore the review of these cases will focus on potential efficacy outcomes only; overdose cases were reviewed for impact on safety as outlined below. Most dosing error cases were missed doses (interruptions). Typically, these dosing errors occurred infrequently, affecting less than 10% of overall exposure. Table 3-1 in the appendix provides a review of 80 cases (infrequent and short episodes of missed doses or underdosing) which are considered unlikely to impact the long-term efficacy outcomes. An additional 8 subjects with infrequently missed doses/underdosing episodes also had overdose episodes and are described in Table 2-2. These 88 cases represent 83 % of all dosing error cases. Safety outcomes were not impacted by brief treatment interruptions. Sixteen subjects had frequently missed doses (>10% of overall exposure) due to dosing errors. These could potentially impact efficacy; a review and analysis of these cases is presented in Table 2-1. The potential impact over time on efficacy outcomes was assessed for individual subjects based on serum ferritin trends as well as

considering dosing errors frequency and duration vs overall time on study treatment. Among 16 subjects, the serum ferritin trend during the study period was overall either stable or decreasing in 11 subjects, in 5/ 16 patients with frequent missed doses, an increasing trend of serum ferritin was observed. Based on the review of AE data, safety outcomes were not impacted by missed doses in these subjects. Table 2-2 provides a review of the overdose cases in 11 subjects with an analysis of the potential impact on safety. Four of them had a single-day overdose episode with marginally increased doses: 14 mg/kg instead of 10.5 mg/kg, 21.1 mg/kg instead of 17.5 mg/kg, 29.8 mg/kg instead of 21 mg/kg, 33.5 mg/kg instead of 28 mg/kg. No AEs were associated with these episodes. The other 7 subjects had either an AE of overdose reported and/or the dose taken was substantially above maximally recommended dose of 28 mg/kg/day. Nevertheless, no major impact on safety was observed in 6 subjects (as no symptoms or AE reported apart from overdose) and one subject with a SAE of overdose with associated symptoms was discharged from the hospital the day after the overdose. Nine of these 11 subjects also had other types of dosing errors (underdosing episodes or missed doses) during the study, which are detailed in the same table as well as Table 2-1 along with review of serum ferritin trend in these subjects. A summary table, counting number of cases is provided in the last Table 2-3.

Discussion:

This overall comprehensive analysis of dosing error cases in 106 subjects indicated that 11 subjects had overdose episodes (defined as dose taken was more than 15% higher than prescribed dose), 16 subjects had frequently missed doses/underdosing (>10% of overall exposure), and 88 subjects (83%) had infrequently missed doses (< 10% of overall exposure); this group includes also some cases where exact start/end date of each missed dose and therefore % of overall exposure was unknown. The impact over time on efficacy outcomes was assessed for individual subjects based on serum ferritin trends, taking into account the type and frequency of dosing errors vs the overall duration of treatment which could be up to 6 years (one year of the core phase and up to 5 years in extension phase). Given the long duration of the study, it is important to note that there could be other factors outside of missed doses that could impact serum ferritin levels. The impact on safety outcomes was assessed based on a review of AE data. Of all the cases reviewed for a potential impact on safety, none had AEs that could be directly associated with dosing errors, except for events associated with one serious overdose case, described in Table 2-2. Among the 11 overdose cases, 4 cases had a single-day overdose episode with marginally increased doses with no AEs reported. The other 7 subjects had either an AE of overdose reported and/or the dose taken was substantially above maximally recommended dose of 28 mg/kg/day. No other AEs reported during or after the overdose event in 6/7 subjects. One subject with a SAE of overdose was discharged from the hospital the day after the overdose without significant adverse outcomes reported, this patient had symptoms consistent with AEs labeled for Exjade. Among the 16 subjects with frequent treatment interruptions due to dosing error (> 10% of overall exposure), which could potentially impact efficacy and SF trends, 11 of them had serum ferritin values that showed a stable or decreasing trend over time, and 5 subjects had serum ferritin results that showed an increasing trend over time. Of note, apart from compliance/dosing errors, treatment efficacy and serum ferritin trends are impacted by other factors such as appropriate dose levels and timely dose adjustments according to serum ferritin trends and individual tolerability, baseline disease and severity of iron overload, RBC transfusion intensity, treatment duration etc. Frequently missed doses in 5 subjects could contribute to insufficient efficacy/an increasing serum ferritin trend, along with other possible factors.

For most subjects (88; 83%), dosing errors were short, infrequent and below 10% of exposure days. Thus, they were unlikely to significantly impact efficacy outcomes during long-term treatment. SF trends were reviewed for all 88 subjects, with only 14 of them reporting an increasing SF trend during the study, and additional 2 subjects discontinued due to lack of efficacy (per investigator assessment), not

associated with dosing errors. The increasing SF trend in 14 subjects could not be directly attributed to these brief and infrequent dosing errors (missed doses and/or underdosing) and were likely driven by other reasons. The remaining 72 subjects had stable and/or decreasing SF trends and 34 patients achieved serum ferritin below 1000 ug/L, which is a target level for transfusion-dependent iron overload conditions.

Conclusion:

After comprehensive review and analysis of dosing errors looking at individual cases, AEs and SF trends, there was no evidence of a significant impact of dosing errors on subjects' safety and efficacy outcomes. Despite dose changes, interruptions, and adjustments, over 90% of the planned dose was taken, showing minimal impact on overall compliance for most subjects.

Assessor's comment:

The MAH provided a comprehensive clinical review of dosing errors, evaluating their safety and efficacy impacts on patients' outcomes.

One hundred six dosing error cases were retrieved. The reported cases were categorized based on the type of dosing error and presented in tables. For missed or underdosing cases which represent most of dosing errors but occurring infrequently in majority (83% of all cases), the data did not indicate any significant impact on safety and the focus was instead on potential efficacy outcomes. In fact, 16 subjects had frequently missed doses and the potential impact on efficacy was assessed through the serum ferritin levels and the error dosing frequency and duration. Stable or decreasing serum ferritin levels were observed in 11 out of the 16 cases. The 5 remaining cases show increasing levels of serum ferritin. This could be explained by the impact of various factors such as baseline disease, severity of iron overload, dose adjustment and treatment duration contributing to insufficient efficacy/increasing serum ferritin levels.

The serum ferritin levels were reviewed also for all the subjects with short and infrequent dosing error. 14 out of 88 subjects experienced an increase on SF likely driven by other reasons then the dosing errors according to the MAH. The remaining 72 subjects had stable and/or decreasing SF trends and 34 patients achieved serum ferritin below 1000 ug/L, which is the target level for transfusion-dependent iron overload.

However, overdose cases were specifically examined for their impact on safety. While missed doses were the most common error, they occurred infrequently and had a minimal effect on overall exposure. Concerning the overdose cases, no AEs were associated with single-day overdose episodes. One subject experienced a SAE of overdose with associated symptoms that fully recovered the following day.

It is important to note that some cases lacked a precise date for the missed doses. Additionally, many of the overdose cases involved other dosing errors (underdosing or missed doses), which preclude accurate impact assessment of dosing errors.

No new safety signal emerged from the assessed data.