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Human Medicines Evaluation Division

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

EXJADE

deferasirox

Procedure no: EMEA/H/C/000670/P46/073

Note

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

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1. Introduction

On 21 October 2016, the MAH submitted a completed paediatric study for deferasirox (EXJADE), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

CHMP's comment
This study has been identified for Art 46 submission as part of a remediation exercise conducted by the MAH, reviewing all interventional and non-interventional studies with paediatric patients in scope of Art 46 requirements.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study CICL670A2201 : *a randomised, open label, multi-center, phase II study to evaluate the safety and efficacy of oral deferasirox 20 mg/kg/day relative to SC deferoxamine in sickle cell disease patients with iron overload from repeated blood transfusions* is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

Exjade is brand name for deferasirox presented as dispersible tablets in 3 doses strengths: 125, 250 and 500mg. The investigational drug was available as tablets at dosage strengths of 125 mg, 250 mg and 500 mg, packaged in high-density polyethylene (HDPE) bottles with an induction seal and child resistant closure.

2.3. Clinical aspects

2.3.1. Introduction

Deferasirox (company research code: ICL670, DFX) is an orally active chelator that is highly selective for iron (III). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Deferasirox promotes excretion of excess iron, primarily in the feces. Deferasirox was developed by Novartis for the treatment of chronic iron overlo ad due to frequent blood transfusions (≥ 7 mL/kg/month of packed red blood cells) in patients with beta thalassemia major aged 6 years and older. It is also indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in the following patient groups:

☐ in pediatric patients with beta thalassemia major with iron overload due to frequent blood transfusions (≥ 7 mL/kg/month of packed red blood cells) aged 2 to 5 years,

☐ in adult and pediatric patients with beta thalassemia major with iron overload due to infrequent blood transfusions (<7 mL/kg/month of packed red blood cells) aged 2 years and older,

☐ in adult and pediatric patients with other anemias aged 2 years and older.

Further it is also indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non - transfusion-dependent thalassemia syndromes aged 10 years and older.

Deferasirox was first registered on 02-Nov-2005 in the United States and subsequently in the EU via centralized procedure on 28-Aug-2006. Deferasirox is currently approved in over 100 countries.

The MAH submitted a final report(s) for:

CICL670A2201 : a randomised, open label, multi-center, phase II study to evaluate the safety and efficacy of oral deferasirox 20 mg/kg/day relative to SC deferoxamine in sickle cell disease patients with iron overload from repeated blood transfusions.

2.3.2. Clinical study

CICL670A2201: a randomised, open label, multi-center, phase II study to evaluate the safety and efficacy of oral deferasirox 20 mg/kg/day relative to SC deferoxamine in sickle cell disease patients with iron overload from repeated blood transfusions.

Description

This study was conducted in 33 centers in 2 countries (Canada and US). First patient enrolled on 12 May 2005 and the last patient completed on 08 Apr 2008.

Methods

Objective(s)

The primary objective of this study was to assess the safety of ICL670 compared to deferoxamine, during 24 weeks, in patients with sickle cell disease and iron overload from repeated blood transfusions.

The secondary objectives were as follows:

• To assess the long-term safety of ICL670, for up to 104 weeks (2 years), in patients with sickle cell disease and iron overload from repeated blood transfusions.

• To assess the safety of ICL670 in a subgroup of the patients receiving concomitant hydroxyurea.

• To evaluate the efficacy of ICL670 versus DFO, after 24 weeks, in patients with sickle cell disease and iron overload from repeated blood transfusions.

• To evaluate the efficacy of ICL670, for up to 104 weeks (2 years), in patients with sickle cell disease and iron overload from repeated blood transfusions.

• To evaluate the pharmacokinetic parameters of ICL670 in patients with sickle cell disease, including patients receiving concomitant hydroxyurea.

• To explore the utility of magnetic resonance imaging (MRI) for assessment of the efficacy of therapy with iron chelators in a sub-set of patients.

CHMP's comment

As a general comment, the investigation of paediatric use was not a primary objective of this study and no specific analysis in paediatric population was performed in the clinical study report.

Study design

Patients were randomized in a 2:1 ratio for a treatment period of 24 weeks to receive either oral DFX at a dose of 20 mg/kg/day once daily or subcutaneous DFO at a total weekly dose of 175 mg/kg for 5 to 7 days. The randomization was stratified by age (≥ 2 to < 12, ≥ 12 to < 16, and ≥ 16 years) and by concomitant administration of hydroxyurea. After the initial 24-week treatment period, all DFO treated patients discontinued DFO and crossed over to receive once daily administration of oral DFX up to Week-52, which was then followed by an extension period during which all patients received DFX until Week-104.

Table 2-1 Study design

Phase	**Screening and Randomization**		**Randomized Period**	**Cross-over Period**	**Extension Period**
Period	**Screening**	**Baseline**	**Phase 1**	**Phase 2**	**Phase 3**
Visit(s)	1	2	3 - 8	9 - 15	16 - 22
Week(s)	-4 to -1	-	1 - 24	25 - 52	53 - 104
Randomization		X			
DFX group		DFX 20 mg/kg/day	DFX 20 mg/kg/day	DFX 20 mg/kg/day	DFX 20 mg/kg/day
DFO group		DFO as per protocol	DFO as per protocol	DFX 20 mg/kg/day	DFX 20 mg/kg/day

Study population /Sample size

A total of 268 patients were screened, and 212 patients were randomized. Nine patients were excluded from the full analyses (due to exclusion of Center 512), and 12 patients did not receive any treatment.

Hence, 191 patients received at least one dose of study medication (135 in DFX and 56 in DFO), and included in the safety analyses. Of the 203 patients, **140 (69.0%) were in the pediatric age range (defined as between 2 to < 18 years for this study).**

Repartition of paediatric patients

In safety set 1, 10 patients are between 2-6 years-old (6 in DFX arm and 4 in DFO arm), 63 patients between 6-12 years old (42 in DFX arm and 21 in DFO arm) and 53 between 12 and 16 years-old (35 in DFX arm and 18 in DFO arm).

In safety set 2, 10 patients are between 2-6 years-old (6 in DFX arm and 4 in cross over arm), 57 patients between 6-12 years old (42 in DFX arm and 15 in cross over arm) and 49 between 12 and 16 years-old (35 in DFX arm and 14 in cross over arm).

CHMP's comment

A majority of patients enrolled in this study are paediatric patients (around 70%). In this study, paediatric population between 2 and 6 years-old is included but the number of children is relatively low (10/140; 7%). No child under 2 years-old was enrolled.

The long term safety in paediatric population (especially in youngest patients: 2-6 years-old) is listed as missing information in the current RMP (V13).

Treatments

Safety set 1

A total of 129 (95.6%) patients were planned to receive 15 - <25 mg/kg/day ICL670; all 129 patients received the planned dose. Although 35 (62.5%) patients were planned to receive 30- <50 mg/kg/day DFO, 50 (89.3%) patients actually received this dosage. No patient received a dosage of ≥ 25 mg/kg/day ICL670 or ≥ 50 mg/kg/day DFO during the first 24 weeks.

The duration of exposure of patients is respectively 5.9 months and 6.2 months for DFX and DFO arm.

Safety set 2:

A total of 154/188 (81.9%) patients in both arms were planned to receive 15 - <25 mg/kg/day ICL670; 150 (79.8%) patients received the planned 15 - <25 mg/kg/day dose. No patient received a dosage of ≥ 35 mg/kg/day ICL670 after start of treatment with ICL670.

The duration of exposure of patients is respectively 21.6 months and 19.6 months for DFX and cross over arm.

CHMP's comment

We regret that the average daily dose (planned/actual) and duration of exposure were not recorded by age group.

As all patients received planned dose between 15-25 mg/kg/day of DFX (mean : 19.8 in SA1 and 21.2 in SA2) and as 70% of patients are paediatrics, it can be estimated that a majority of paediatric patients received roughly the approved dose of 20mg/kg/day of DFX.

Outcomes/endpoints

Serum ferritin, total iron, and transferrin will be measured at screening and at every study visit on the chemistry blood samples sent to the central laboratory. These values will be monitored as efficacy parameters. In addition, the change in serum ferritin values obtained during the study will serve as a secondary endpoint for efficacy analysis.

Safety assessment was based on descriptions of AEs and SAEs occurring in this study as well as clinical laboratory data for hematology, blood chemistry, SF, total iron, transferrin, urinary protein, urinary creatinine, viral serology (hepatitis B and C) and pregnancy testing. Height and weight of patients were also evaluated for safety.

Other safety evaluations included ECG, ECG/holter monitoring, ocular examination and audiometry.

Statistical Methods

The primary variables were adverse events (AEs) and laboratory parameters : AE data were summarized descriptively by treatment group using number and frequencies for categorical variables, while summary statistics of laboratory data (means, median, standard deviation, ranges) as well as shift tables and listings for patients with notable laboratory values were provided.

The primary efficacy variable was the absolute change in serum ferritin. Summary statistics and graphical displays of serum ferritin measurements as well as absolute and relative changes from baseline were provided by treatment group. Absolute and relative change from baseline was summarized by age category, splenectomy and hydroxyurea category, and by treatment group. For the first 24 weeks, a two-sided 95% confidence interval of the mean difference in the absolute change between ICL670 and DFO arms was calculated with adjustment of stratification factors (age and hydroxyurea) and the amount of transfused blood during the study. For week 52 and week 104, twosided 95% confidence intervals of the average change were calculated for the ICL670 arm as well as for all the patients also with adjustment of age, hydroxyurea and amount of transfusion. An exploratory mixed model (time and treatment as fixed factors and patient as a random factor) analysis was done using all available serum ferritin values to compare the change over time of serum ferritin between the two treatment arms in the first 24 weeks, as well as to assess the change over time of serum ferritin from start of ICL670 to end of study.

The pre-dose and 2-hour post-dose levels of deferasirox and Fe-[ICL670]2 obtained in this study were summarized descriptively by hydroxyurea therapy group. Descriptive statistics included mean, SD, CV, geometric mean, CV geometric mean, min, max and median.

Results

Recruitment / Number analysed

For the 24 week period (FA-1 Set), the majority (96.1%) of patients were Black. More than half (56.2%) were female. Of the 203 patients, 140 were pediatric patients (<18 years); 92/135 (68.1%) pediatric patients in DFX and 48/68 (70.6%) pediatric patients in DFO group. More than 80% (116 patients, 82.9%) of the 140 pediatric patients were between 6 and <16 years of age; 77/92 (83.7%) in the pediatric DFX group and 39/48 (81.2%) in the pediatric DFO group

At start of treatment with DFX (FA-2 set), the majority of patients (96%) were Black and more than half (56.4%) were female. Of the 188 patients, 130 (69.1%) were pediatric patients; 92/135 (68.1%) pediatric patients in DFX and 38/53 (71.6%) were in cross-over group. More than 80% (106 patients, 81%) of the 130 pediatric patients were between 6 and <16 years of age; 77/92 (83.7%) in the pediatric DFX group and 29/38 (76.3%) in the pediatric DFO group.

CHMP's comment

A majority of patients enrolled in this study are paediatric patients (around 70%). In this study, paediatric population between 2 and 6 years-old is included but the number of children is relatively low (10/140; 7%). No child under 2 years-old was enrolled.

Efficacy results

According to the MAH, there was a similar reduction in serum ferritin observed in the DFX and DFO treatment groups during the first 24-week period and in the cross-over group after the start of DFX treatment, although there was a numerically greater reduction observed in the DFO group in the first 24 weeks; the differences observed between DFX vs. DFO and the cross-over group was less pronounced as the study progressed (could be due to start of DFX treatment in crossover group). The mean (± SE) change in serum ferritin from baseline (adjusted for amount of transfused blood) was -

146.7 (± 266.75) mg/mL at Week 24, -487.3 (± 138.83) mg/mL at Week 52 and -682.6 (±205.06) mg/mL at Week 104 for the DFX group

Efficacy in paediatric population:

At first 24-weeks, an overall decreasing trend for all age categories similar to overall population, although the variability was high and the number of patients was small for some of the age categories (Table 4-1).

In the DFX treatment arm, the decrease was more pronounced in 16 to ≤ 18 years age group (but number of patients in this treatment group is low) while it was more evident in 6 to ≤ 12 years age group for DFO treatment arm. It is important to note that in the 6 to ≤ 12 years age group there appears to be a mean increase in serum ferritin over the first 24 weeks of treatment with DFX. However, this was possibly due to the effect a single high ferritin value in one patient.

Table 4-1 Change from baseline to week 24 in serum ferritin (ug/L) by age category – First 24 weeks (PP– 1 set)

Age categories (years)	DFX N=117	DFO N=50	All patients N=167
Age 2-<6			
N	6	3	9
Mean* (SE)	-191.3 (254.88)	-134.6 (362.94)	-172.4 (191.58)
95% CI	-814.9 – 432.4	-1022.7 -753.4	-625.4 – 280.6
Ages 6-<12			
N	37	15	52
Mean (SE)	518.7 (767.46)	-1564.7 (1206.47)	-82.3 (654.17)
95% CI	-1023.5 – 2061.0	-3989.2 – 859.8	-1396.2 – 1231.7
Ages 12-<16			
N	32	13	45
Mean (SE)	-357.5 (182.04)	-644.1 (286.29)	-440.3 (152.73)
95% CI	-724.8 – 9.9	-1221.9 - -66.4	-748.3 - -132.3
Age 16-<18#			
N	6	5	11
Mean (SE)	-633.8 (335.0)	-236.0 (366.99)	-453.0 (242.37)
95% CI	-1406.4 - 138.7	-1082.3 - 610.3	-1001.3 - 95.3
Ages 16-<50			
N	41	18	59
Mean (SE)	-675 (264.5)	-508.3 (399.22)	-624.2 (218.77)
95% CI	-1204.9 - -145.2	-1308.0 – 291.4	-1062.3 - -186.1
Ages 50-<65			
N	1	1	2
Mean (SE)	-	-	-614.8 (0.00)
95% CI	-	-	-

Source: [Appendix 1–Table 1-1.a], [Appendix 1–Table 2-1.a]
#Additional analysis done for age category 16 to <18 years to comply with EMA pediatric definition.
*Means are adjusted for amount of transfused blood.

For pediatric patients, in months 3 to 6, the mean absolute changes in serum ferritin were - 171.4 (±506.92), 33.1 (±1885.21), and -271.2 (±1039.28) mg/mL for ICL670 patients aged 2- <6, 6-<12, and 12-<16 years, respectively; for DFO patients, the mean changes were -131.5 (±467.22), -1153.1 (± 2971.39), and -578.5 (±660.23) mg/mL respectively

After start of treatment with DFX, an overall decreasing trend continued for all age categories except for 16 to <18 years where increase was observed, this could be due to high variability, less number of patients (2 to 6 and 16 to <18), and possible outliers. Hence, no definitive conclusions can be made. In the DFX arm, the decrease was more pronounced in 2 to <6 years while it was more evident in 12

to <16 years for cross-over group at week 52 (Table 4-2). There were no meaningful differences in the change in serum ferritin at 104-week after the start of DFX treatment patients.

Table 4-2 Change from start of treatment with DFX to week 52 in serum ferritin (ug/L) by age category–After start of treatment with DFX (PP-2 set)

Age categories (years)	DFX N=113	Cross-over N=49	All patients N=162
Ages 2 - <6			
N	6	4	10
Mean (SE)	-681.0 (221.45)	-481.8 (271.24)	-601.3 (164.10)
95% CI	-1204.6 – -157.3	-1123.2 – 159.6	-979.7 - -222.9
Ages 6 - <12			
N	35	10	45
Mean (SE)	-436.2 (194.96)	-423.7 (364.74)	-433.4 (169.93)
95% CI	-829.7 - -42.8	-1159.8 – 312.4	-776.1 - -90.7
Ages 12 - <16			
N	32	13	45
Mean (SE)	-509.2 (198.42)	-627.9 (311.53)	-543.5 (165.48)
95% CI	-909.6 - -108.8	-1256.6 – 0.8	-877.2 - -209.8
Ages 16 - <18#			
N	7	3	10
Mean (SE)	414.7 (802.60)	-94.7 (1229.64)	261.9 (632.06)
95% CI	-1483.1 - 2312.6	-3002.3 - 2812.9	-1195.6 - 1719.4
Ages 16 - <50			
N	39	12	51
Mean (SE)	-490.5 (331.47)	-334.1 (603.39)	-453.7 (285.79)
95% CI	-1157.0 – 175.9	-1547.2 – 879.1	-1028.0 – 120.6
Ages 50 - <65			
N	1	1	2
Mean (SE)			-1889.4 (0.00)
95% CI			

Source: [Appendix 1 - Table 1-1.b], [Appendix 1 - Table 2-1.b]
#Additional analysis done for age category 16 to <18 years to comply with EMA pediatric definition.
*Means are adjusted for amount of transfused blood

For all pediatric patients after the start of ICL670 treatment, in months 21 to 24, the mean absolute changes in serum ferritin were -1025.2 (±887.77), -277.7 (±1833.16), and -651.2 (±1388.79) mg/mL for patients aged 2-<6, 6-<12, and 12-<16 years, respectively. An overall decreasing trend was observed for all age categories, although the variability was high and the number of patients was small for some of the age categories.

According to the MAH, age has no clinically relevant influence on the absolute change of SF seen with ICL treatment.

CHMP's comment

No specific analysis of paediatric efficacy was specified as a protocol objective.

At first 24-weeks, an overall decreasing trend for all age categories similar to overall population. However the variability was high and the number of patients was too small for some of the age categories (Ages 2-<6; age 16-<18) to draw any conclusion. In the 6 to ≤ 12 years age group there appears to be a mean increase in serum ferritin over the first 24 weeks of treatment with DFX. According to the MAH, this was possibly due to the effect of one patient's single high ferritin value.

After start of treatment with DFX, an overall decreasing trend continued for all age categories except for 16 to <18 years where increase was observed. In the same way, no definitive conclusions can be made due to the small size of sample.

Safety results

According to the MAH, in overall population, DFX appeared to be well tolerated when comparing the adverse event (AE) profiles of DFX and DFO. The AEs reported in study with DFX were similar to those observed in other studies with DFX. Fewer AEs were observed in the DFX-treated patients than in the DFO-treated patients during the first 24 weeks of treatment. The observed AEs are in line with those expected from this treatment in this condition/population.

Safety in pediatric patients

According to the MAH, in the pediatric population, DFX was also well tolerated when comparing the AE profile across DFX, DFO and cross-over treatment groups. AEs reported in all age categories were consistent with the safety profile observed in other studies with DFX as well as with established safety profile of DFX.

There were very few pediatric patients in the age group 2 to <6 years, hence the safety evaluation is focused on 6 to <12, 12 to <16, and 16 to <18 years age group. Due to small sample size in 16 to <18 years group the results should be interpreted with caution. For reporting purpose, all percentages are calculated based on total number of patients in each treatment group.

1- Safety during the 1st 24-weeks of treatment (safety-1 set)

Table 3-1 Summary of AEs, deaths, SAEs and other significant AEs in DFX-treated patients by age category- First 24 weeks (Safety- 1 set)

	DFX N[1]=135 Age category (years)					
	2- <6 N = 6 n* (%)	6- <12 N = 42 n (%)	12- <16 N = 35 n (%)	16- <18# N = 9 n (%)	16- <50 N = 50 n (%)	50- <65 N = 2 n (%)
All AEs	6 (4.4)	28 (20.7)	27 (20.0)	8 (5.9)	47 (34.8)	2 (1.5)
AEs suspected to study drug	0	9 (6.7)	3 (2.2)	3 (2.2)	22 (16.3)	2 (1.5)
Number of deaths [1]	0	0	0	0	0	1(0.7)
Serious adverse events	1 (0.7)	5 (3.7)	9 (6.7)	4 (3.0)	23 (17)	2 (1.5)
AEs leading to discontinuation [2]	0	1 (0.7)	0	0	2 (1.5)	0
AEs leading to dose adjustment or temporary interruption	0	7 (5.2)	3 (2.2)	0	10 (7.4)	1 (0.7)

[1] Death information comes from "end of treatment" CRF page.
[2] Only events with suspected relationship to study drug are summarized.
N[1] = total number of patients in the DFX arm
*n % is out of total N[1]=135
#Additional analysis done for age category 16 to <18 years to comply with EMA pediatric definition.
Source: [Appendix 1-Table 2.2-1.a], [Appendix 1-Table 2.2-3.a], [Appendix 1-Table 2.2-5.a], [Appendix 1- Table 2.2-6.a], [Appendix 1 - Table 2.2-8.a], [Appendix 1 - Table 2.2-9.a], [Appendix 1 - Table 3.2-1.a], [Appendix 1 - Table 3.2-4.a], [Appendix 1 - Table 3.2-5.a], [Appendix 1 - Table 3.2-6.a]

Adverse events by system organ class and preferred terms

Overall, incidence of AEs was low in pediatric patients compared to adults.

The incidence of AEs were less frequent in the DFX-treated patients than in the DFO-treated patients during the first 24 weeks of treatment across all age groups; 6 to <12 (20.7% vs. 26.8%), 12 to <16 (20% vs. 21.4%), 16 to <18 (5.9% vs. 8.9%).

In the Safety-1 set (first 24-weeks), the most commonly affected SOCs across all age groups were: gastrointestinal disorders, infections and infestations, nervous system disorders, general disorders and administration site conditions.

☐ In 6 to <12 years age group, the most frequently reported AEs by preferred term (PT) occurring in >5% of DFX-treated patients were; vomiting (5.9%), headache (5.9%), pyrexia (5.9%), and rash (6.7%).

☐ In 12 to <16 years age group, headache (6.7%) was the most frequently reported AE by PT occurring in >5% of DFX-treated patients.

☐ In 16 to <18 years age group, diarrhoea (3.0%), and nausea (3.0%) was the most frequently reported AE by PT occurring in ≥3% of DFX-treated patients.

Suspected adverse events

Overall, incidence of suspected AEs was low in pediatric patients compared to adults.

☐ In 6 to <12 years age group, suspected AEs were reported in 6.7% DFX-treated patients and 8.9% DFO-treated patients. The most frequently reported suspected AEs by PT occurring in more than one DFX-treated patient were; diarrhoea, alanine aminotransferase (ALT) increased, liver function test abnormal, and rash.

☐ In 12 to <16 years age group, only 3 patients in DFX treatment arm (mainly GI disorders : nausea, diarrhea, gastrooesophageal reflux disease and LFT abnormal) and four patients in DFO-treatment arm (mainly injection site disorders) reported suspected AEs.

Adverse events by severity

Majority of the maximum severity AEs were mild to moderate in both treatment arms across all age groups.

☐ In 6 to <12 years age group, mild to moderate severity AEs were reported in 24 (17.8%) DFX-treated patients. Only four patients (3.0%) in DFX arm reported severe AEs.

☐ In 12 to <16 years age group, mild to moderate severity AEs were reported in 21 (15.5%) DFX-treated patients. Severe AEs were reported in only 6 (4.4%) DFX-treated patients.

☐ In 16 to <18 years age group, mild to moderate severity AEs reported in 5 (3.7%) DFX treated patients. Severe AEs were reported in 3 (2.2%) patients.

Serious adverse events and Deaths

Overall, very few patients experienced severe AEs (SAEs) in both treatment arms during first 24-weeks across all age groups. No deaths were reported in pediatric patients.

☐ In 6 to <12 years age group, 5 (3.7%) patients in DFX, and 5 (8.9%) patients in DFO treatment arm have reported SAEs;. Pyrexia was the most common SAE by PT reported in more than one DFX-treated patient.

☐ In 12 to <16 years age group, SAEs were reported in 9 (6.7%) DFX-treated patients and 5 (8.9%) DFO-treated patients. The most common SAEs by PT occurring in >2% of DFX treated patients were sickle cell anaemia with crisis (3%), and pyrexia (2.2%).

☐ In 16 to <18 years age group, SAEs were reported in 4 (3.0%) DFX-treated patients and 2 (3.6%) DFO-treated patients. Sickle cell anaemia with crisis (2.2%) was the most common SAE by PT occurring in >2% of DFX-treated patients.

In the 6 to 12, and 12 to 16 years age groups, only one SAE (liver function abnormality) was reported (one in each age group) to be study drug related in the DFX group. No study drug related SAE was reported in both age groups in the DFO arm.

Adverse events leading to study drug discontinuation

Study-drug related AEs leading to discontinuations were uncommon in pediatric population with only one patient in 6 to <12 age group (2 AEs reported for 1 patient) leading to study discontinuation due to increased ALT and aspartate aminotransferase (AST). No patients in the other pediatric age groups (2 to <6, 12 to <16, 16 to <18) experienced suspected AEs leading to study drug discontinuation.

Adverse events leading to dose adjustment or interruptions

AEs leading to dose adjustment or study drug interruptions were infrequent in pediatric population. In the DFX treatment group, 7 (5.2%) patients in 6 to <12 age group and 3 (2.2%) patients in 12 to <16 age group had AEs which required dose adjustment or interruptions. The most frequent reason for study drug adjustments in the 6 to <12 age groups were abnormal liver function (including ALT/AST increased). No patients experienced AEs leading to dose adjustment or study drug interruptions in 16 to <18 years age group in the DFX arm.

Hematology and clinical chemistry

No clinically significant difference in the frequency of absolute neutrophil count, platelet count, ALT/AST increased, abnormal serum creatinine or urinary protein/creatinine ratios values was observed between DFX, and DFO treatment groups across all pediatric age categories. Increase of AST during study > upper limit of normal (ULN) when baseline is <ULN seems to occur more often compared to ALT, however this effect is seen across all age groups and across treatments.

CHMP's comment
No new safety concern emerges from the safety data observed within the 1st 24 weeks of DFX therapy.

2- Safety after start of treatment with DFX (Safety-2 set)

Table 3-2 Summary of AEs, deaths, SAEs and other significant AEs DFX-treated patients by age category- After start of treatment with DFX (Safety-2 set)

	DFX N[1]=135 Age category (years)					
	2- < 6 N = 6 *n (%)	6- < 12 N = 42 n (%)	12- < 16 N = 35 n (%)	16 - <18# N = 9 n (%)	16- < 50 N = 50 n (%)	50- < 65 N = 2 n (%)
All AEs	6 (4.4)	37 (27.4)	35 (25.9)	9 (6.7)	49 (36.3)	2 (1.5)
AEs suspected to study drug	1 (0.7)	12 (8.9)	6 (4.4)	4 (3.0)	31 (23.0)	2 (1.5)
Number of deaths [1]	0	0	0	0	0	1 (0.7)
Serious adverse events	2 (1.5)	18 (13.3)	18 (13.3)	7 (5.2)	38 (28.1)	2 (1.5)
AEs leading to discontinuation [2]	0	1(0.7)	1(0.7)	0	5 (3.7)	0
AEs leading to dose adjustment or temporary interruption	1 (0.7)	12 (8.9)	6 (4.4)	2 (1.5)	15 (11.1)	2 (1.5)

[1] Death information comes from "end of treatment" CRF page.
[2] Only events with suspected relationship to study drug are summarized.

Adverse events by system organ class and preferred terms

In the Safety-2 set (patients who received at least one dose of DFX), infections and infestations and gastro-intestinal disorders were the most commonly affected SOCs in the pediatric population across all age groups. The incidence of AEs were similar in DFX-treated patients (started with DFX right from the beginning of the study) compared to the cross-over group in 6 to <12 group (27.4% vs. 28.3%), 16 to <18 (6.7% vs.7.5%) and was slightly higher in 12 to <16 group (25.9% vs. 22.6%).

☐ In 6 to <12 years age group, the most frequently reported AEs by PT occurring in >5% of DFX-treated patients were; headache (13.3%), pyrexia (11.1%), cough (8.9%), vomiting (8.1%), rash (7.4%), abdominal pain (7.4%), pain in extremity (6.7%), upper respiratory tract infection (5.2%), diarrhoea (5.2%), nausea (5.2%), and oropharyngeal pain (5.2%). In the cross-over group; pyrexia (15.1%), upper respiratory tract infection (9.4%), cough (9.4%), headache (9.4%), abdominal pain (5.7%), pneumonia (5.7%), back pain (5.7%) and nasal congestion (5.7%) were the most frequently reported AEs by PT occurring in >5% of cross-over patients.

☐ In 12 to <16 years age group, pyrexia (13.3%), headache (10.4%), oropharyngeal pain (7.4%), pain in extremity (7.4%), back pain (6.7%), cough (5.9%), abdominal pain (5.9%), nausea (5.2%), rash (5.2%), nasopharyngitis (5.2%), pain (5.2%), diarrhoea (5.2%) and sickle cell anaemia with crisis (5.2%) were most frequently reported AEs by PT occurring in >5% of DFX-treated patients. In the cross-over group; upper respiratory tract infection (5.7%), vomiting (5.7%), headache (5.7%), cough (5.7%), back pain (5.7%) and oropharyngeal pain (5.7%) were the most frequently reported AEs by PT occurring in >5% of cross-over patients.

☐ In 16 to <18 years age group, nausea (4.4%), vomiting (3.7%), diarrhoea (3.7%), sickle cell anaemia with crisis (3.7%) were the most frequently reported AEs by PT DFX-treated patients. In the cross-over group; chest pain (5.7%), hypersensitivity (3.8%), headache (3.8%), pyrexia (3.8%), and

arthralgia (3.8%) were the most frequently reported AEs by PT occurring in >3% of cross-over patients.

Suspected adverse events

In 6 to <12 years age group (after start of DFX), 12 patients (8.9%) in the DFX group and 3 patients (5.7%) in the cross-over group had reported suspected AEs. The most frequently reported suspected AEs by PT occurring >2% DFX-treated patients were ALT (3.0%), AST (2.2%) increased, abnormal liver function test (2.2%), and rash (2.2%).

In 12 to <16 years age group, 6 patients (4.4%) in DFX treatment group and one patient (1.9%) in cross-over group had AEs which was suspected to study drug.

Adverse events by severity

Majority of the maximum severity AEs were mild to moderate in both treatment arms after start of treatment with DFX across all age groups.

☐ In 6 to <12 years age group (after start of DFX), mild to moderate severity AEs were reported in 25 (18.6%) DFX-treated patients, and 10 (18.8%) patients in cross-over group. Severe AEs were reported in 12 (8.9%) DFX-treated patients, and 5 (9.4%) patients in the cross-over group.

☐ In 12 to <16 years age group, mild to moderate severity AEs were reported in 20 (14.8%) DFX-treated patients, and 8 (15.1%) patients in cross-over group. Severe AEs were reported in 15 (11.1%) DFX-treated patients, and 4 (7.5%) patients in cross-over group.

☐ In 16 to <18 years age group, mild to moderate severity AEs reported in 3 (2.2%) DFX treated patients, and 2 (3.8%) patients in cross-over group. Severe AEs were reported in 6 (4.4%) DFX-treated patients, and 2 (3.8%) patients in cross-over group.

Serious adverse events and Deaths

Overall, very few patients experienced SAEs in both treatment groups after start of treatment with DFX across all age categories. No deaths were reported in pediatric patients.

☐ In 6 to <12 years age group (after start of DFX), 18 (13.3%) patients in DFX, and 5 (9.4%) patients in cross-over group have reported SAEs. Pyrexia was the most common SAE reported in 6 (4.4%) DFX-treated patients, and in 4 (7.5%) cross-over patients.

☐ In 12 to <16 years age group, SAEs were reported in 18 (13.3%) DFX-treated patients and 4 (7.5%) patients in cross-over group. The most common SAEs occurring in >2% of DFX treated patients were sickle cell anaemia with crisis (5.2%), pyrexia (4.4%), abdominal pain (2.2%), and sickle cell anaemia with crisis (3.8%) occurring in >2% of cross-over patients.

☐ In 16 to <18 years age group, SAEs were reported in 7 (5.2%) DFX-treated patients and 3 (5.7%) cross-over patients. Sickle cell anaemia with crisis (3.0%) was the most common SAE occurring in >2% of DFX-treated patients. In the cross-over group, no AE reached the 3% threshold.

Two (1.5%) patients each in 6 to <12 (liver function abnormalities) and 12 to <16 age group (liver function abnormalities, increased serum ferritin and rash) experienced an SAE that was suspected to be study drug related by the Investigator. No patients in cross-over group reported suspected SAEs.

Adverse events leading to study drug discontinuation

After start of treatment with DFX, one patient in 6 to 12 (DFX group) and 2 patients in the 12 to 16 age group (one in DFX and one in cross-over group) had suspected AEs leading to discontinuation from the study. The most commonly reported suspected AEs leading to discontinuations were liver function abnormalities including AST or ALT increased. Other reasons were cataract and increased serum ferritin. No patients experienced suspected AEs leading to study drug discontinuation in 16 to <18 years age group.

Adverse events leading to dose adjustment or interruptions

After start of treatment with DFX, 12 (8.9%), 6 (4.4%), and 2 (1.5%) patients had AEs leading to dose adjustment or study drug interruption in 6 to ≤ 12, 12 to ≤ 16, and 16 to ≤ 18 years age group, respectively for patients in the DFX group. For cross-over patients, this was the case for one patient in the 6 to ≤ 12, no patient in the 12 to ≤ 16 and two patients in the 16 to ≤ 18 years age group. Majority of AEs were related to liver function abnormalities.

Hematology and clinical chemistry

No clinically significant difference in the frequency of absolute neutrophil count, platelet count, ALT/AST increased, abnormal serum creatinine or urinary protein/creatinine ratios values was observed between DFX, and cross-over treatment groups across all age categories.

CHMP's comment

No new safety concern emerges from the safety data observed after the start of DFX therapy.

The long term safety in paediatric population (especially in youngest patients : 2-6 years-old) is listed as missing information in the current RMP (V13). In this study, paediatric population between 2 and <6 years-old is included but the number of children is relatively low (10/140; 7%). A total of 2 serious cases were reported (one TIA not related and one streptococcal/parvovirus infection, both considered not suspected). No conclusion can be drawn from these data. Of note, no child under 2 years-old was enrolled.

2.3.3. Discussion on clinical aspects

In the Study A2201, overall there were no unexpected safety findings in the pediatric population following treatment with deferasirox. Data from the pediatric patients indicate an efficacy and safety profile that is aligned with adult population and similar to the known clinical profile of deferasirox.

No specific analysis of pediatric efficacy was specified as a protocol objective.

An overall decreasing trend for all age categories similar to overall population. However the variability was high and the number of patients was too small in each age categories to make definitive conclusion.

There are no new safety concerns observed. Overall incidence of AEs, SAEs, and AE leading to discontinuation was lower in pediatric patients compared to the adult patients. Both deaths that occurred in this study were in adult patients. This study did not bring any new information on the long term use in the youngest patients (2 - <6 years-old) due to the low number of patients of this age range enrolled.

In conclusion, the benefit-risk assessment for deferasirox remains unchanged for the currently approved indications. No changes to the pediatric information of the current deferasirox EU SPC are proposed.

3. Rapporteur's overall conclusion and recommendation

This study has been identified for Art 46 submission as part of a remediation exercise conducted by the MAH, reviewing all interventional and non-interventional studies with paediatric patients in scope of Art 46 requirements.

The investigation of paediatric use was not a primary objective of this study and no specific analysis for efficacy and safety in paediatric population was performed in the clinical study report.

An overall decreasing trend for all age categories similar to overall population. However the variability was high and the number of patients was too small in each age categories to make definitive conclusion.

There were no unexpected safety findings in the pediatric population following treatment with deferasirox. This study did not bring any new information on the long term use in the youngest patients (2 - <6 years-old) due to the low number of patients of this age range enrolled.

In conclusion, the benefit-risk assessment for deferasirox remains unchanged for the currently approved indications. No changes to the pediatric information of the current deferasirox EU SPC are proposed.

4. MS comments

During the procedure we have received MS 1 and MS 2 comments. We have not received any comments from other MS:

- **MS 1** agrees with the rapporteur's conclusions and have no further comments.
- **MS 2 comments** :

  In general we can agree with the conclusions as stated by the Rapporteur for the above mentioned procedure. However, we would kindly ask you whether you have considered to provide an integrated report and discussion of the 3 current paediatric worksharing procedures, as it may facilitate decision-making regarding any amendments that might be needed in the SmPC for paediatric patients.

CHMP's comment

After discussion with EMA, it was necessary to have 3 different assessment reports as the applicant submitted P46 071, P46 072 and P46 073 as three separate eCTD sequences (0144, 0145 and 0146 respectively) on 17/10 for P46071 and P46 072 and on 20/10/2017 for P46 073.

However, it could be highlighted that, in all 3 procedures, we are not recommending any PI changes.

☒ Fulfilled:

No regulatory action required.