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Procedure Management and Committees Support Division

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

Exjade

deferasirox

Procedure no.: EMA/H/C/000670/P46

Note

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

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1. Introduction

On 20 April 2016, the MAH submitted one completed paediatric studies for Exjade®, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that this study 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

The orally active, tridentate iron chelator deferasirox (company research code: ICL670) is the active ingredient in Exjade® dispersible tablets. Exjade is currently approved in over 100 countries. In the European Union, it was approved on 28-Aug-2006 for the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older.

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

- in paediatric patients with beta thalassaemia major with iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) aged 2 to 5 years,

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

- in adult and paediatric patients with other anaemias aged 2 years and older.

Since 20 December 2012, Exjade has been also indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients 10 years and older with nontransfusion- dependent thalassaemia syndromes.

The MAH submitted the final report for this clinical study and a clinical overview of this study.

The MAH submitted one final report for:

- CICL670ATR04: a phase II, multi-center, single-arm, prospective study to evaluate the safety and efficacy of deferasirox in beta thalassemia major patients after hematopoietic stem cell transplantation (HSCT).

2.3.2. Clinical study

CICL670ATR04: A phase II, multi-center, single-arm, prospective study to evaluate the safety and efficacy of deferasirox in beta-thalassemia major patients after hematopoietic stem cell transplantation

Description

This is a phase II, multi-center, single-arm, prospective study to evaluate the safety and efficacy of deferasirox in beta thalassemia major patients after hematopoietic stem cell transplantation (HSCT). The study was conducted in 9 study centers in Turkey.

Methods

Objective(s)

Primary objectives:

The primary objective of the present study was to determine the safety; incidence, type and severity of adverse events including renal, hepatic, biochemistry and hematologic parameters of deferasirox in the treatment of iron overload after HSCT in patients with betathalassemia major in 12 months period.

Secondary objectives:

The secondary objectives were:

- To evaluate the change in serum ferritin level from baseline to 12th month
- To evaluate the change in the further parameters of iron overload (cardiac iron and liver iron concentration by MR examination) from baseline to 12th month
- To determine the percentage of patients reaching serum ferritin levels lower than 500 µg/L at week 28 and week 52

Study design

This study is a prospective, single-arm, multi-center, local, phase II clinical study. The patients received oral deferasirox at an initial dose of 10 mg/kg/day and dose escalation was allowed up to 20 mg/kg daily for 12 months or until the serum ferritin level was below 500 µg/L. Dose titration was allowed in 3 months periods by 5 mg/kg/day at the discretion of the investigator unless any AE's were observed, which may create additional risk to the patient. During the 12 months treatment period, patients were evaluated every 28 days. After the completion of the study, patients were treated at the physician's discretion with the current best treatment options. The study started on 19-Sep-2013 and completed on 21-Oct-2015 (last patient last visit). The study was conducted in 9 study centers in Turkey.

Study population /Sample size

Beta-thalassemia patients between the age of 3 and 17 who had iron overload after HSCT were included in the study. The estimated sample size was 30 patients.

Inclusion criteria

- Male or female patients aged >2 and <18 years
- Patients who had HSCT for beta-thalassemia major
- HSCT was performed minimum 6 months and maximum 2 years ago
- The washout period after the immunosuppressive therapy should be at least 3 months
- Significant IOL should be present including:
    - Serum ferritin >1000 µg/L or
    - cardiac MRI <20 ms or
    - liver iron concentration ≥ 5 mg/g dry weight measured by R2* MRI
- Informed consent obtained by the child's legal guardians

Exclusion criteria

- Patients who have any contraindication for treatment with deferasirox according to the prescribing information
- Patients who depend on transfusion
- Patients with clinical symptoms of cardiac dysfunction (shortness of breath at rest or exertion, orthopnea, exercise intolerance, lower extremity edema, arrhythmias)
- Patients who are experiencing severe complication of HSCT (e.g. acute GVHD)
- Severe concomitant illnesses (e.g. cancer, active AIDS)
- Patients involved in a clinical trial with another compound
- Patients who received any other chelation including experimental drugs after the HSCT
- Patients unable to undergo study assessments including MRI, e.g. who are claustrophobic to MRI, have a cardiac pacemaker, ferromagnetic metal implants other than those approved as safe for use in MR scanners (Example: some types of aneurysm clips, shrapnel), and patients who are obese (exceeding the equipment limits).
- Illicit drug use and/or alcohol use (defined as no more than one drink a day for women, and no more than two drinks a day for men within the 12 months prior to enrolment. A standard drink is generally considered to be 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of 80-proof distilled spirits)
- Patients who received phlebotomy for treatment

- Significant medical condition interfering with the ability to take part in this study (e.g. systemic uncontrolled hypertension, unstable cardiac disease not controlled by standard medical therapy,) systemic disease (cardiovascular, renal, hepatic, etc.)
- Significant proteinuria as indicated by a urine protein: urine creatinine ratio > 0.5 mg/mg in a non-first void urine sample at screening visit 1 or screening visit 2
- Calculated creatinine clearance ≤ 60 ml/min on two measurements during screening visit 1 and screening visit 2
- Serum creatinine > ULN on two measurements during screening visit 1 and screening visit 2
- ALT >3 x ULN at screening visit 1 or screening visit 2
- Clinical evidence of active hepatitis B (positive HBsAg with negative HBsAb) or hepatitis C (positive HCV antibody and detectable HCV RNA with ALT above the normal range)
- Known diagnosis of cirrhosis (confirmed by biopsy if available)
- Concomitant therapy with hydroxyurea, erythropoietin, butyrate
- A history of clinically relevant ocular and/or auditory toxicity related to iron chelation therapy
- History of positive HIV serology (ELISA)
- Presence of a surgical or medical condition that might significantly alter the absorption, distribution, metabolism or excretion of the study drug
- Patients with active inflammatory diseases that may interfere with the accurate measurement of serum ferritin
- Pregnant or breast feeding patients
- History of non-compliance with medical regimens or patients who are considered potentially unreliable and/or not cooperative, unwilling or unable to comply with the protocol
- History of hypersensitivity to any of the study drug or excipients
- Patients with considerable impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral deferasirox / ICL670 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)

Treatments

The investigational study drug used in the course of this single arm trial is deferasirox (ICL670).

All patients were treated with deferasirox 10 mg/kg daily. The dose might be increased gradually up to 20 mg/kg/day. Dose increase was done at least in 3 month intervals by 5 mg/kg/day at the discretion of the investigator. After dose titration, serum creatinin, BUN, ALT, AST, proteinuria, adverse events was assessed in at least after 5 days and in 2 weeks.

Deferasirox (ICL670) was provided as 125 mg, 250 mg, and 500 mg dispersible tablets packaged in high density polyethylene (HDPE) bottles with induction seals and child resistant closures labeled.

Medication labels complied with the legal requirements of the country where the study was implemented and was printed in the local language. The storage conditions and the expiration date for study drug was described on the medication label.

Novdrug capsules were supplied to the investigators at dose strengths of Exjade 125 mg, Exjade 250 mg and Exjade 500 mg.

Outcomes/endpoints

Statistical Methods

Data were analyzed using the PASW 18.0 for Windows program. Descriptive statistics were expressed as numbers and percentages for categorical variables and as mean, standard deviation, minimum, maximum, lower quartile, upper quartile and median for numerical variables. The variables were investigated using visual (histogram, probability plots) and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Friedman test and Wilcoxon Signed Rank test were conducted to test whether there is a significant change in the serum ferritin level. The Wilcoxon test was performed to test the significance of pairwise differences using Bonferonni correction to adjust for multiple comparisons.

The Kaplan-Meier survival estimates were calculated for grouped adverse events (defined by MedDRA System Organ Class terms). A p value <0.10 was considered statistically significant.

Results

Recruitment/ Number analysed

Beta-thalassemia patients between the age of 3 and 17 who had iron overload after HSCT were included in the study. The estimated sample size was 30 patients.

Overall 27 pediatric patients with beta thalassemia after HSCT were screened and 26 patients completed the study. One patient was lost to follow-up.

The mean age (SD) was 9.07 (3.81) years with a range from 3 to 16 years. A higher percentage of patients were male (70.4%). All patients were Caucasians. The mean (SD) body mass index (BMI) of the patients was 17.03 (2.37) kg/m2 (Table 2-1).

Table 2-1 Patient demographics

Patient characteristic		Deferasirox N=27
Age (years)	Mean	9.07
	SD	3.81
	Median	9.00
	Range (Min.-Max.)	3.00-16.00
Age group – n (%)	2-6 years	8 (29.6)
	7-11 years	12 (44.4)
	≥ 12 years	7 (25.9)
Gender – n (%)	Male	19 (70.4)
	Female	8 (29.6)
Race – n (%)	Caucasian	27 (100.0)
BMI (kg/m^2)	Mean	17.03
	SD	2.37
	Median	16.46
	Range (Min.-Max.)	13.71-21.94

Baseline data

At baseline, 8 patients (29.6%) had other medical disorders besides the study indication (Table 2-2).

Table 2-2 Medical history or medical condition of the patients at baseline

		Frequency	Percent
Any medical history or current medical condition not related to the study indication at baseline?	No	19	70.4
	Yes	8	29.6
History condition	Elevated liver enzymes	2	22.2
	Anemia	1	11.1
	Bone Marrow Transplantation	1	11.1
	Minimal mitral insufficiency	1	11.1
	Pulmonary hypertension	1	11.1
	Splenectomy	2	22.2
	Flu	1	11.1
	Total	**9**	**100.0**

The mean age (SD) of patients at beta thalassemia diagnosis was 13.19 (18.91) months. The mean duration from diagnosis to study entry (SD) was 100.81 (48.59) months and the duration from diagnosis to HSCT was 86.45 (49.19 months).

Table 2-3 History of beta thalassemia major

Months	Mean	SD	Minimum	Maximum	Percentile 25	Percentile 75	Median
Age of diagnosis	13.19	18.91	2.33	98.14	4.90	12.55	7.39
Duration from diagnosis to study visit	100.81	48.59	25.89	188.16	62.13	140.58	93.96
Duration from diagnosis to HSCT	86.45	49.19	10.12	179.22	48.33	121.10	75.50

At baseline, 2 patients (7.4%) had T2*(magnetic resonance imaging) MRI < 20 msec and 23 patients (85.2%) had R2*MRI≥ 5 mg/g dry weight.

Table 2-4 T2*MRI and R2*MRI range of the patients at baseline

		Frequency	Percent
T2*MRI Range	< 20 msec	2	7.4
	≥ 20 msec	25	92.6
	Total	**27**	**100.0**
R2*MRI Range	≥ 5 mg/g dry weight	23	85.2
	< 5 mg/g dry weight	4	14.8
	Total	**27**	**100.0**

The mean (SD) serum ferritin concentration was 1766.81 (599.64) ng/mL [Table 14-2 of CICL670ATR04 CSR]. Overall, 6 patients (22.2%) were using concomitant medications at baseline [Table 12-4 of CICL670ATR04 CSR].

Efficacy results

The median serum ferritin levels significantly decreased from 1718 ng/mL to 845.30 ng/mL from baseline to week 52 (p<0.001).

Table 4-1 Change in serum ferritin level from baseline to month 12

	N	Median (Min.-Max.)	*p*-value
Baseline	27	1718.00 (873.70-2919.00)	
V1 (Week 4)	27	1775.00 (549.80-4023.00)	
V3 (Week 6)	27	1729.00 (813.00-3100.00)	
V5 (Week 8)	27	1737.00 (764.20-3340.00)	
V6 (Week 10)	27	1723.00 (790.00-5840.00)	
V7 (Week 12)	27	1575.00 (752.70-8671.00)	
V8 (Week 16)	26	1540.00 (620.00-3155.00)	
V9 (Week 20)	26	1374.00 (578.00-2883.00)[a]	<0.001
V10 (Week 24)	26	1274.00 (450.30-3000.00)[a]	
V11 (Week 28)	26	1246.50 (359.00-2907.00)[a]	
V12 (Week 32)	26	1222.00 (302.80-2884.00)[a]	
V13 (Week 36)	26	1025.50 (277.40-2549.00)[a]	
V14 (Week 40)	26	1153.50 (196.00-2296.00)[a]	
V15 (Week 44)	25	1141.00 (196.70-2465.00)[a]	
V16 (Week 48)	25	932.40 (156.10-2070.00)[a]	
Final Evaluation (Week 52)	**27**	**845.30 (146.20-2740.00)[a]**	

Efficacy was also measured with cardiac iron and liver iron concentration by MRI examination. An increase in median T2*MRI range was observed, though not significant, which was probably due to small sample size ($p=0.50$). A significant decrease was measured in liver iron overload ($p<0.001$): median R2*MRI change from 8.60 (2.80-43.00) at baseline to 4.10 (0.90-12.50) at week 52.

Table 4-2 Changes in T2*MRI and R2*MRI from baseline to week 52

		N	Median (Min.-Max.)	*p*-value
T2*MRI (Cardiac MRI)	S1 (Week 0)	27	25.95 (4.50-41.00)	0.520
	FE (Week 52)	24	28.00 (18.50-44.00)	
R2*MRI (Liver MRI)	S1 (Week 0)	27	8.60 (2.80-43.00)	<0.001
	FE (Week 52)	25	4.10 (0.90-12.50)	

FE: final evaluation; MRI: magnetic resonance imaging
Source: CSR Table 14-4, 14-6

Two patients (7.7%) reached serum ferritin levels lower than 500 µg/L at week 28 and 9 (33.3%) at week 52.

Table 4-3 Percentage of patients reaching serum ferritin levels lower than 500 µg/L at week 28 and week 52

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	Serum Ferritin	n (%)
V11 (Week 28)	≥500 ng/mL	24 (92.3)
	<500 ng/mL	2 (7.7)
Final Evaluation (Week 52)	≥500 ng/mL	18 (66.7)
	<500 ng/mL	9 (33.3)

Source: Table 14-3

Taken together, these results indicate that deferasirox is effective in decreasing iron overload in beta-thalassemia major patients after HSCT.

Assessor's comment

This study was not designed to assess deferasirox efficacy. Efficacy parameters were assessed as second objectives.

The changes in serum ferritin levels were first assessed from baseline to 12th month. Comparison of liver iron concentration by MRI examination before and after transplantation should be more relevant to assess efficacy as the serum ferritin levels could be higher (effect due ton inflammation) in the first year after transplantation. Serum ferritin levels decreased with deferasirox but this effect became significant from baseline since Week 20. This effect is sustained until Week 48 but the result should be taken with cautions because of the limited number of patients and the high difference between the lower and upper bounds of the serum ferritin median range in each patients visit. Finally, a percentage of 33.3% of patients reaching serum ferritin levels lower than 500 %g/l at the final evaluation visit (Week 52).

This study failed to demonstrate an improvement of cardiac iron overload (Cardiac MRI: 25.95 vs. 28.00; p=0.520). However, a decrease of liver iron overload could be observed from baseline to Week 52 (Liver MRI: 8.6 vs. 4.1; p<0.001).

In conclusion, data collected in this study allow to document efficacy data of deferasirox in a specific pediatric population but should be taken with cautions as only 27 patients were included in this study among 9 study centers in Turkey.

Safety results

AEs regardless of study-drug relationship were reported in 92.6% of patients. In the patients experiencing AEs, the most commonly affected primary SOCs were infections & infestations (51.9%), respiratory, thoracic and mediastinal disorders (48.1%), investigations (44.4%), general disorders (33.3%) and administration site conditions and gastrointestinal disorders (33.3%).

Table 3-2 Incidence of AEs by primary system organ class (Safety set)

Primary system organ class	Exjade N=27 n (%)
Patients with at least one AE	25 (92.6)
Infections and infestations	14 (51.9)
Respiratory, thoracic and mediastinal disorders	13 (48.1)
Investigations	12 (44.4)
General disorders and administration site conditions	9 (33.3)
Gastrointestinal disorders	9 (33.3)
Blood and lymphatic system disorders	7 (25.9)
Skin and subcutaneous tissue disorders	3 (11.1)
Immune system disorders	2 (7.4)
Eye disorders	1 (3.7)
Metabolism and nutrition disorders	1 (3.7)
Musculoskeletal and connective tissue disorders	1 (3.7)

Source: CSR Table 14-9

The most common AEs, regardless of causality, were anemia (25.9%), alanine aminotransferase (ALT) increased (25.9%), cough (25.9%), pyrexia (25.9%), aspartate aminotransferase (AST) increased (22.2%), pharyngitis (22.2%), influenza (18.5%), diarrhea (11.1%) and vomiting (11.1%).

Table 3-3 Incidence of AEs by preferred term (PT) (Safety set)

	Exjade N=27 n (%)
Patients with at least one AE	25 (92.6)
Anemia	7 (25.9)
Alanine aminotransferase increased	7 (25.9)
Cough	7 (25.9)
Pyrexia	7 (25.9)
Aspartate aminotransferase increased	6 (22.2)
Pharyngitis	6 (22.2)
Influenza	5 (18.5)
Diarrhoea	3 (11.1)
Vomiting	3 (11.1)
White blood cell count decreased	2 (7.4)
Influenza like illness	2 (7.4)
Upper respiratory tract infection	2 (7.4)
Eczema	2 (7.4)
Haemophilus infection	2 (7.4)
Herpes zoster	2 (7.4)
Hypersensitivity	2 (7.4)
Infection	2 (7.4)
Rhinorrhea	2 (7.4)
Sinusitis	2 (7.4)
Urinary tract infection	1 (3.7)
Pneumonia	1 (3.7)
Abdominal pain	1 (3.7)
Abdominal pain upper	1 (3.7)
Breath sounds	1 (3.7)
Bronchiolitis	1 (3.7)
Bronchitis	1 (3.7)
Bronchopneumonia	1 (3.7)
Conjunctivitis	1 (3.7)
Dry skin	1 (3.7)
Ear infection	1 (3.7)
Epistaxis	1 (3.7)
Eye infection	1 (3.7)
Gastroenteritis rotavirus	1 (3.7)
Gingival abscess	1 (3.7)

	Exjade N=27 n (%)
Hepatic enzyme increased	1 (3.7)
Hordeolum	1 (3.7)
Lung infection	1 (3.7)
Nasal congestion	1 (3.7)
Nausea	1 (3.7)
Neck pain	1 (3.7)
Oral herpes	1 (3.7)
Oropharyngeal pain	1 (3.7)
Platelet count decreased	1 (3.7)
Protein urine present	1 (3.7)
Pyoderma	1 (3.7)
Rash	1 (3.7)
Stoma site infection	1 (3.7)
Vision blurred	1 (3.7)
Vitamin D deficiency	1 (3.7)

Source: CSR Table 14-8

Overall, 7.5% (10 out of 134) of the AEs were suspected to be drug-related [Table 12-10 of CICL670ATR04 CSR].

No action was taken in 37.3% of the AEs (50 out of 134). For 4.5% of the AEs, the study drug was adjusted or temporarily interrupted and medication was administered following 58.2% of the AEs [Table 12-11 of CICL670ATR04 CSR].

During the study, 8 AEs were grade 3 (increase in ALT in 3 patients, increase in AST in 2 patients, decrease in platelet count in 1 patient, herpes zoster in 1 patient and pneumonia in 1 patient) in 7.9% of patients [Table 12-12 of CICL670ATR04 CSR].

Time to onset of AEs was analyzed by PT and are presented in Table 12-13 of CICL670ATR04 CSR. Increase in liver enzymes (ALT and AST) occurred at a median of 28 and 30 days, respectively, and anaemia occurred at a median of 28 days. The median duration of ALT and AST increase was 28 days [Table 12-14 of CICL670ATR04 CSR].

Assessor's comment

The MAH did not provide a table with AEs related to study drug.

Deaths, other serious adverse events and other significant adverse events

There were no deaths during the study.

During the study, 3 patients experienced 6 serious adverse events (SAEs). None of them was considered to be drug-related. The respective narratives are provided below:

- Prior to start of deferasirox treatment, a pediatric patient had elevated liver function tests and concomitant medication including ursodeoxycholic acid. On 14-Jan-2014, the subject experienced flu like symptoms, fever and bronchial infection which resulted in hospitalization on the same day. It was reported that the subject's flu like symptoms, fever and bronchial infection were possibly due to influenza virus type B, and treatment with Enfluvir and Sulperazon was started. On 15-Jan-2014, the subject's laboratory test included influenza virus type B-PCR which was found to be positive (normal value-normal). On 17-Jan-2014, the

subject received the first dose of deferasirox at a dose of 10 mg/kg/day. On 20-Jan-2014, he completely recovered from the event and was discharged from the hospital. On 25-Feb-2014, the subject was hospitalized for his routine annual control, laboratory tests were normal and was discharged from the hospital on26-Feb-2014. The investigator assessed the event (fever, flu-like symptoms, bronchial infection (influenza virus type B)) as serious (hospitalization). The investigator did not suspect a relation between the event (fever, flu like symptoms, bronchial infection (influenza virus type B) and the study medication as the study treatment was not started prior to the onset of the event. The investigator also stated that the subject was hospitalized for his annual control after "HSCI" and this hospitalization was not relevant to the study treatment. Although the patient experienced ALT and AST increased at two measurement points, they were Grade 1 and 2 events, and required no action.

- A pediatric subject with a medical history of gallbladder sludge. He had bronchitis (grade 2) and was taking Augmentine, when treatment was started with deferasirox at a dose of 10 mg/kg/day on 20-Jan-2014. The subject underwent allogeneic bone marrow transplantation due to beta thalassemia. On 03-Mar-2014, his ALT (846 IU/L; grade 4) and AST levels (1008 IU/L; grade 4). On 05-Mar-2014, the subject was diagnosed with viral hepatitis B, the patient received Zeffix, and treatment with study medication was temporarily interrupted for one month due to event. Investigator reported that the event improved after study medication was interrupted. On 10-Mar-2014, AST was 1098 IU/L grade 4, ALT was 743 IU/L grade 3, serology test including HBsAG was performed which was positive at a value of 25.63 (grade 2) and anti HBs value was less than 5 (grade 2). On 25-Mar-2014, AST was 60 IU/L and ALT was 59 IU/L. On 16 Apr 2014, AST was 50 IU/L (normal value: 10 to 40) CTCAE grade 1 and ALT was 19 IU/L (normal value: 8 to 40) CTCAE grade 1. The event was assessed as serious (medically significant) by the investigator. The investigator confirmed that the event was not due to progression of the underlying disease. The other possible contributory factor for ALT and AST increase included hepatitis B infection. The investigator did not suspect a causal relationship between the event and the study medication. The investigator gave a rationale that the etiologic cause of liver dysfunction, hepatitis B, tested positive in the subject. Hence the drug was considered as not related to liver dysfunction.
- Prior to start of deferasirox treatment, a pediatric patient presented on 9-Dec-2013 with neutrophil count decreased (0.49 x 109/L, neutropenia grade 4) with no hospitalization. On 10-Dec-2013, the subject started treatment with 125 mg deferasirox twice daily. On 18-Dec-2013, the subject was reported to have infection and received treatment with Augmentin. No action was taken with regard to the study medication due to this event. On 23-Dec-2013, neutropenia was resolved. On 26-Dec-2013, the subject completely recovered from neutropenia grade 4 and infection and the hemoglobin value was 1.876/mm3. The investigator assessed the events as serious (medically significant) and did not suspect any relationship between the event and study medication. In summary, the patient had neutropenia before the start of the study drug, and he had neutropenia and anemia Grade 1 and 2 at some measurement points throughout the study.

Four patients experienced 6 AEs that led to study drug adjustment or temporary discontinuation:

- One patient experienced diarrhoea and vomiting
- One patient had ALT and AST increased
- One patient had ALT increased

- One patient experienced hepatic enzymes increased, which was considered to be drug related by the investigator.

All AEs required dose adjustment or temporary discontinuation recovered to Grade 1 or less.

Clinical laboratory evaluation

Creatinine increased levels (33% increase from baseline (BL) and above upper limit of normal (ULN) at two consecutive visits at least 5 days apart) was observed in 1 patient (3.7%)

Increase in proteinuria was observed in 9 patients (33.3%) [Table 14-11 and 14-14 of CICL670ATR04 CSR].

ALT increased levels (BL ALT<ULN, 3X BL/5X ULN) were recorded in 9 patients (33.3%) and AST increased levels (BL AST ≥ULN, 3X BL/5X ULN) in 3 patients (11.1%) [Table 14- 14 and 14-15 of CICL670ATR04 CSR].

Decrease in absolute neutrophil count (<1.5 x 109/L) was observed in 6 patients (22.2%): two patients had severe neutropenia (0.53 x 109/L and 0.49 x 109/L); one of them reported as SAE: Decrease in platelet count (<100 x 109/L) was observed in 2 patients (7.4%) [Table 14- 12 and 14-13 of CICL670ATR04 CSR].

Assessor's comment

The safety population, with subjects from the FAS having had at least one safety assessment post baseline, consisted of 25 patients.

Research in the line listing of AEs by patient find 10 adverse events related to study medication in 4 patients (14.8%): 6 ALT increased (three grade 3 with two of them resulted on study drug dosage adjusted/temporarily interrupted, one grade 2 resulted on study drug dosage adjusted/temporarily interrupted and two grade 1), 2 AST increased of grade 3 with one of them of them resulted on study drug dosage adjusted/temporarily interrupted, one hepatic enzyme increased of grade 2 resulted on study drug dosage adjusted/temporarily interrupted and one urinary tract infection of grade 1.

In this study, elevation of transaminase was the most reported AEs related to study drug medication and was seen in 4 (14.8%) patients. This frequency is higher than reported in the SmPC for the overall population, for which elevations of transaminases were reported in 2% of patients.

Overall, there were no deaths during the study and no unexpected safety findings.

Discrepancies regarding the number of drug adjustment or temporary discontinuation are noted between table 12-18 and 12-19 of the clinical overview and the line listing of AEs by patient. Research in the line listing find 4 patients with 8 AEs that led to study drug adjustment or temporary discontinuation whereas in the table 12-18 and 12-19 the reported number is 4 patients with 6 AEs.

The most frequently reported AEs which led to study drug adjustment or temporary discontinuation was elevation of transaminase (6AEs of 8AEs).

MAH's conclusion

Overall, there were no unexpected safety findings in the 27 pediatric patients with beta thalassemia after HSCT following treatment with deferasirox dispersible tablets up to a dose of 20 mg/kg daily for 12 months. Incidence, type and severity of AEs including renal, hepatic, biochemistry and hematologic parameters are consistent with the known safety profile of deferasirox.

Median serum ferritin levels and liver iron overload (measured with R2*MRI) significantly decreased during the course of the study indicating that deferasirox at doses between 10 to 20 mg/kg/day is effective in decreasing iron overload in beta thalassemia major pediatric patients after HSCT.

In conclusion, the benefit-risk assessment for deferasirox remains positive for the currently approved indications and justifies continuation of the development program in pediatric patients.

No changes to the pediatric information of the current deferasirox Core Data Sheet are proposed as a result of this study and no regulatory consequences of the submitted study are anticipated for the pediatric information in the EU SmPC.

Assessor's comment

Efficacy

Concerning efficacy data, the ferritin levels were assessed as second objectives and should be used as supportive data.

Safety

Type and severity of AEs including renal, hepatic, biochemistry and hematologic parameters are consistent with the known safety profile of deferasirox.

In this study, incidence of elevation of transaminases (4 patients, 14.8%) were higher than reported in the SmPC for the overall population, for which elevation of transaminases were reported in 2% of patients.

However, these data should be taken with cautions as only 27 patients were included in this study among 9 study centers in Turkey.

2.3.3. Discussion on clinical aspects

Patients with homozygous beta thalassemia require chronic blood transfusions to survive; however, ineffective erythropoiesis and transfusions cause iron overload that is ultimately fatal if not continuously treated. The only available alternative therapy is hematopoietic cell transplantation (HCT).

Persistence of tissue iron overload can cause significant morbidity and mortality, such as that seen in hereditary hemochromatosis. Progression of liver disease to cirrhosis has been documented in some patients in the years after transplantation. Thus, iron removal by phlebotomy (the first treatment

because of the potential toxicity of oral chelators especially when combined with cyclosporine) or chelation is indicated in all transplanted thalassemic patients who have evidence of hepatic iron overload.

The objective of this procedure is to comply with Article 46 of Regulation (EC) No 1901/2006 that requires any marketing authorization holder-sponsored studies which involve the use in the pediatric population of a medicinal product covered by a marketing authorization, whether or not they are conducted in compliance with an agreed pediatric investigation plan, to be submitted to the competent authority.

Study CICL670ATR04 is a MAH-sponsored study that has been recently completed and qualifies for Article 46 submission. This was a phase II, multi-center, single-arm, prospective study to evaluate the safety and efficacy of deferasirox in beta thalassemia major patients after hematopoietic stem cell transplantation (HSCT).

Concerning efficacy data, the ferritin levels were assessed as second objectives and should be used as supportive data.

The changes in serum ferritin levels were first assessed from baseline to 12th month. Comparison of liver iron concentration by MRI examination before and after transplantation should be more relevant to assess efficacy as the serum ferritin levels could be higher (effect due to inflammation) in the first year after transplantation. Serum ferritin levels decreased with deferasirox but this effect became significant from baseline since Week 20. This effect is sustained until Week 48 but the result should be taken with cautions because of the limited number of patients (n=25) and the high difference between the lower and upper bounds of the serum ferritin median range in each patients visit. Finally, a percentage of 33.3% of patients reaching serum ferritin levels lower than 500 µg/l at the final evaluation visit (Week 52).

This study failed to demonstrate an improvement of cardiac iron overload (Cardiac MRI: 25.95 vs. 28.00; p=0.520). However, a decrease of liver iron overload could be observed from baseline to Week 52 (Liver MRI: 8.6 vs. 4.1; p<0.001).

Finally, the primary objective of the present study was to determine the safety; incidence, type and severity of adverse events including renal, hepatic, biochemistry and hematologic parameters of deferasirox in the treatment of iron overload after HSCT in patients with beta-thalassemia major in 12 months period.

A total of 25 patients comprised the Safety set. Ten AEs related to study medication were found in 4 patients (14.8%). The drug related AEs reported in the pediatric population were ALT increased, AST increased, hepatic enzyme increased and urinary tract infection.

In this study, elevation of transaminases were the most reported AEs related to study drug medication and were seen in 4 (14.8%) patients. This frequency is higher than reported in the SmPC for the overall population, for which elevations of transaminases were reported in 2% of patients.

In conclusion, data collected in this study allow to document safety data of deferasirox in beta-thalassemia major patients after hematopoietic stem cell transplantation (HSCT) but should be taken with cautions as only 27 patients were included in this study among 9 study centers in Turkey.

Based on the data provided, we can conclude that no unexpected safety findings were identified. A higher frequency of elevation of transaminases related to study drug medication was seen in this study than reported in the SmPC for the overall population whereas in this study a decrease of liver iron overload could be observed from baseline to Week 52. However, this occurred in a very limited population of patients with expected severity of AE. No further regulatory action are required from this procedure.

3. CHMP's overall conclusion and recommendation

☒ **Fulfilled:**

No regulatory action required.