26 March 2020
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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: EMEA/H/C/000670/P46/078

Note

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

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List of abbreviations used in the text

AE	Adverse event
DT	Dispersible Tablet
ECG	Electrocardiogram
EMA	European Medicines Agency
EU	European Union
FAS	Full Analysis Set
FCT	Film-coated tablet
FDA	Food and Drug Administration
ICT	Iron Chelation Therapy
MDS	Myelodysplastic syndrome
RBC	Red blood cells
SAE	Serious adverse event
SmPC	Summary of product characteristics

1. Introduction

This report covers the following post-authorisation commitment undertaken by the MAH: the results from the final analysis of Study CICL670AIC04 (An open-label, multi-center, phase III to collect additional efficacy and safety data with deferasirox film-coated tablets in patients completing study CICL670F2201).

The objective of this submission is to comply with Article 46 of Regulation (EC) No 1901/2006 which requires any study of a medicinal product with a marketing authorization in the European Economic Area (EEA) that includes pediatric patients, whether or not the study is conducted in compliance with an agreed pediatric investigation plan, to be submitted to the European Medicines Agency (EMA).

A short critical expert overview has also been provided.

Submission date:	14 January 2020
Start of procedure:	27 January 2020
Rapporteur's preliminary assessment report circulated on:	02 March 2020
CHMP adoption of conclusions:	26 March 2020

2. Scientific discussion

2.1. Information on the development program

CICL670AIC04 study was an interventional study to collect additional data on safety and efficacy of Exjade® (deferasirox) film coated tablet (FCT) formulation in patients with transfusion dependent thalassemia or myelodysplastic syndrome (MDS) (very low, low or intermediate risk) when treated over 24 weeks in CICL670F2201 study. CICL670F2201 study was a randomized, open label, multicenter, 2-arm, phase II study initiated to assess the safety of the DT and the FCT formulations in patients with transfusion-dependent thalassemia or MDS (very low, low or intermediate risk) treated over 24 weeks. Treatment duration of 24 weeks in CICL670F2201 study was considered sufficient to assess the safety, pharmacokinetics and patient reported outcomes of the two formulations. Previous studies of pediatric and adolescent patients demonstrated differences in iron chelation medication compliance within this time period (Jordan et al 2012, Alvarez et al 2009). The CICL670AIC04 study was planned to include up to 58 patients at ages 10 years and older, from all European regions participating sites completed the 24-week treatment under protocol CICL670F2201

This study allowed for the enrollment of male and female patients > 10 years old. This report only focuses on the results of the 3 pediatric patients enrolled in the CICL670AIC04 study. The study started (first patient first visit) on 16-Aug-2016 and completed on 23-Jul-2019 (last patient last visit). The study was conducted at 14 centers across 3 countries (Austria: 1, Greece: 3, and Italy: 10).

No changes to the pediatric information of the current deferasirox Core Data Sheet (CDS) are proposed as a result of this study.

2.2. Information on the pharmaceutical formulation used in the studies

The marketed formulation i.e deferasirox film-coated tablets of 90 mg, 180 mg and 360 mg dose strengths were administered by oral daily dosing.

2.3. Clinical aspects

2.3.1. Introduction

Chronic iron overload represents a serious complication of potentially lifesaving blood transfusions, which are the mainstay of therapy in transfusion-dependent anemias. Since humans have no mechanism for the active elimination of iron from the body, excess iron received via transfusions deposits in various tissues of the body, particularly the liver, heart and endocrine organs, leading to end-organ dysfunction and eventually organ failure. Indeed, organ failure due to chronic iron overload represents the major cause of death in patients with β-thalassemia major who receive blood transfusions regularly without appropriate chelation therapy.

Beta-thalassemias are a group of hereditary blood disorders characterized by anomalies in the synthesis of the beta chains of hemoglobin resulting in variable phenotypes, ranging from severe anemia to clinically asymptomatic individuals. Patients with β-thalassemia major usually present within the first 2 years of life with severe anemia requiring regular red blood cell (RBC) transfusions. Regular transfusion therapy leads to iron overload with iron-related complications including endocrine complications, such as growth retardation, failure of sexual maturation, diabetes mellitus, cardiac complications, such as dilated myocardiopathy, and liver complications including fibrosis and cirrhosis.

Myelodysplastic syndromes (MDS) include a diverse group of acquired disorders of hematopoiesis, collectively characterized by bone marrow failure (i.e. inadequate production of healthy, mature blood cells) and a tendency for clonal evolution. Signs and symptoms of MDS relate to hematopoietic failure, manifesting in anemia, thrombocytopenia or leukopenia. The anemia is often severe, leading to regular transfusions and reduced QoL. Additionally, iron overload may negatively impact survival in MDS, especially for patients with low-risk MDS.

Deferasirox dispersible tablet (DT) was first registered on 02-Nov-2005 in the United States and subsequently in the EU via centralized procedure on 28-Aug-2006. The new deferasirox film-coated tablet (FCT) formulation for oral administration was developed due to the chronic nature of chelation therapy and the importance of patient compliance. Novartis is currently Marketing Authorisation Holder (MAH) for deferasirox DT in 127 countries and for deferasirox FCT in 80 countries worldwide. The FCT used in this study contained the same active substance of the iron chelator deferasirox (Exjade® company research code ICL670) and strength-adjusted to achieve comparable exposure to the currently approved DT. The FCT is available in 3 dose strengths (90 mg, 180 mg and 360 mg) and is dosed based on body weight. The deferasirox FCT can be taken either on an empty stomach or with a light meal. The FCT formulation is

approved in US (30-Mar-2015) and Canada (24-Feb-2016), and in the EU (European Commission Decision dated 22-Mar-2016).

EXJADE is indicated for the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older.

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

- in 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.

Deferasirox is also indicated for the treatment of chronic iron overload in patients with non-transfusion-dependent thalassemia syndromes aged 10 years and older.

EXJADE 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 thalassaemia syndromes aged 10 years and older.

2.3.2. Clinical study

This open-label, multicenter, single arm, 24-month, phase III study was aimed to collect additional data on safety and tolerability as well as data on efficacy of the FCT formulation in patients with transfusion-dependent thalassemia or MDS (very low, low or intermediate risk) when treated for more than 24 weeks in CICL670F2201 study.

Methods

Study design

This open-label, multicenter, single arm study was aimed at collecting additional data on safety and tolerability as well as data on efficacy of the FCT formulation in patients with transfusion dependent thalassemia or MDS (very low, low or intermediate risk) when treated for >24 weeks in CICL670F2201 study. At the start of this study, the following were required to be conducted:

- Patients continuing directly from CICL670F2201 where they were originally randomized to the deferasirox FCT formulation, were required to continue treatment at the same dose they were assigned at the end of CICL670F2201.
- Patients continuing directly from CICL670F2201 who were originally assigned to the deferasirox DT formulation were required to switch to the deferasirox FCT formulation with a dose equivalent to the deferasirox DT dose they were assigned at the end of CICL670F2201.

- Patients who completed CICL670F2201 study and switched to commercially available DT or other ICT were required to undergo a 5-day washout period and then had to use an equivalent FCT starting dose corresponding to their last deferasirox dose on CICL670F2201 study.

Patients were instructed to swallow deferasirox FCT (available strengths of deferasirox FCT tablets: 90 mg, 180 mg and 360 mg) once daily either on an empty stomach or with a light meal.

The planned duration of treatment in this study was for a maximum of 24 months. Dose adjustment was allowed based on serum ferritin levels and investigator's judgment, if necessary every 3 months, with ±3.5 to 7 mg/kg/day, but no more than 28 mg/kg/day.

Patients who were withdrawn prematurely from CICL670F2201 study were not enrolled. Patients with a lag period between completion of CICL670F2201 study and enrollment in this study could be done, after a washout period, even if they had to switch to DT or other chelation therapy in this period. However, no patient for this study continued directly from CICL670F2201 study and the gap time between when patients completed CICL670F2201 and started CICL670AIC04 was often extensive, therefore Principle Investigator's clinical judgment in starting dose assignment was considered acceptable and no protocol deviations was raised for these cases.

The Full Analysis Set (FAS) comprised of all patients enrolled in this study. Analysis of efficacy was done in FAS. The Safety Set comprised of all enrolled patients who received at least one dose of study treatment (deferasirox FCT) and had at least one safety assessment on or after Day 1. The safety analyses was performed on the Safety Set.

Study population /Sample size

A maximum of 58 patients at ages 10 years and older were planned to be enrolled and a total of 53 patients were enrolled from 3 countries across Europe: 3 patients (5.7%) from Austria, 10 patients (18.9%) from Greece and 40 patients (75.5%) from Italy. All 53 patients were included in both the Full Analysis Set (FAS) and the safety set.

Diagnosis and main criteria for inclusion:

- Completed 24-weeks of study treatment as described in protocol CICL670F2201.
- Tolerated deferasirox treatment as per the Investigator's opinion.
- Male and female patients aged ≥ 10 years with either transfusion-dependent thalassemia and iron overload requiring deferasirox DT at doses of ≥ 30 mg/kg/day as per the Investigator's decision, or myelodysplastic syndrome (MDS) of very low, low or intermediate risk as determined by the Revised International Prognostic Scoring System (IPSS-R) and iron overload requiring deferasirox DT at doses of ≥ 20 mg/kg/day as per the Investigator's decision.
- History of transfusion of at least 20 PRBC units and anticipated to be transfused with at least 8 units of PRBCs annually during the study.
- Serum ferritin >1000 ng/mL at Screening.

Key exclusions included

- Creatinine clearance below the contraindication limit in the locally approved prescribing information.
- Serum creatinine >1.5 × ULN at Screening.
- Significant proteinuria as indicated by a urinary protein/creatinine ratio >0.5 mg/mg in a non-first void urine sample at Screening.

Study objectives and related endpoints:

Objectives	Endpoints
Primary objective:	**Primary endpoint:**
To evaluate the overall safety of deferasirox FCT formulation in patients with transfusion-dependent thalassemia or MDS at very low, low or intermediate risk.	Frequency and severity of AEs and changes in laboratory values of interest i.e. serum creatinine and creatinine clearance.
Secondary objective:	**Secondary endpoint:**
To evaluate efficacy of deferasirox FCT on serum ferritin levels (decrease or maintenance, according to the individual therapeutic goal).	Absolute and relative change in serum ferritin level over time.

Statistical Methods

The analyses were descriptive. No hypothesis was tested.

The incidence of any TEAEs overall and by severity were summarized using frequency counts, percentages of patients, and on selected TEAE summaries 95% CIs for percentages obtained using Clopper-Pearson method. Laboratory data were summarized using descriptive statistics including 95% CI of the mean for raw values and absolute change from baseline at each visit. Furthermore, mean and standard deviation (SD) values were plotted over time for each of the laboratory parameters of interest (serum creatinine, creatinine clearance, ALT/SGPT, AST/SGOT, RBC, platelets, WBC total). Serum ferritin was summarized using descriptive statistics of raw values, absolute change from baseline, and relative change from baseline at each visit. The summaries included n, mean with respective 95% CI, SD, minimum, Q1, median, Q3, and maximum.

Results

Demographic characteristics: A total of 53 patients were enrolled in the present study, of those 3 patients (5.7%) were under the age of 18 years (13, 15 and 16 years respectively) and 50 patients (94.3%) were aged ≥ 18 years (86.8% were between the ages of 18 and <50 years; 1.9% were between 50 and <65 years and 5.7% were 65 years or older). Most patients were of Caucasian race (50 patients, 94.3%). Overall, 66.0% of patients were female.

Background characteristics: Most patients (49 patients, 92.5%) had transfusion dependent thalassemia and 4 patients (7.5%) had MDS: all the 3 patients aged <18 years had thalassemia as their main underlying disease. Bone marrow examinations were only performed on patients with MDS (4 patients, 7.5%) and all 4 patients

were found to be hematologically stable. The mean (SD) duration since the last bone marrow examination was 2.6 (1.0) years.

Compliance: Patients had a mean relative consumed tablets count of 90.175% (95% CI: 87.398- 92.951).

CHMP comment

The majority of patients (94.3%) enrolled in this study were adults, and only 3 (5.7%) patients aged <18 years were included.

Efficacy results:

The results of the 3 pediatric patients are provided as follow:

Patient ITA-1276-00005 started treatment with deferasirox FCT at 900 mg/day and daily dose was increased to 1170 mg on Study Day 120 due to lack of efficacy. After Month 7, a decrease in serum ferritin levels was observed as compared with baseline. Starting from Month 14, serum ferritin levels were below <1000 µg/L, thus deferasirox FCT dose was reduced to 1080 mg/day and later 720 mg/day as per protocol during the study. However serum ferritin levels were 1107 µg/L at Month 26.

Patient ITA-1276-00008 started treatment with deferasirox FCT at 1260 mg/day and daily dose was increased to 1530 mg on Study Day 148 and 1710 mg on Study Day 234 due to AE serum ferritin increased. After Month 14, a decrease in serum ferritin levels was observed as compared with baseline. During the study serum ferritin levels were below <1500 µg/L starting from Month 14, and later serum ferritin levels are decreased below $\leq$500 μg/L starting from Month 21 to Month 24, thus deferasirox FCT dose was reduced to 1260 mg/day as per protocol during study. However serum ferritin levels were 573 µg/L at Month 26.

Patient ITA-1276-00011 started treatment with deferasirox FCT at 990 mg/day and daily dose was increased to 1170 mg on Study Day 30 (as per protocol) and 1260 mg on Study Day 75 due to lack of efficacy. This patient experienced an AE of serum ferritin abnormal on Study Day 143 which was ongoing at the time of last reporting.

CHMP comment

The efficacy investigation was the secondary objective of the CICL670AIC04 study. The Absolute and relative change in serum ferritin level over time were provided for each pediatric patients separately.
Out of 3 patients, 2 patients completed the study and 1 patient discontinued due to unsatisfactory therapeutic effect. No efficacy conclusion can be drawn from the 3 pediatric patients enrolled in this study.

Safety evaluation

The most frequent AEs (>50% incidence by system organ class) reported during the treatment with deferasirox FCT were related to infections and infestations in 75.5% of patients (by PT influenza, rhinitis, gastroenteritis, pharyngitis and urinary tract infection occurred in >10% of patients) followed by GI disorders in 67.9% of patients (by PT diarrhea, nausea, vomiting, abdominal pain upper and abdominal pain occurred in >10% of patients).

Approximately 50.9% of patients had a maximum AE grade of moderate and 26.4% of patients had a maximum AE grade of severe. None of the patients had severe gastrointestinal AEs. Maximum AE grading

incidence of moderate (22 patients and 5 patients; 41.5% and 9.4%) or severe (12 patients and 2 patients; 22.6% and 3.8%) was reported among patients who have received deferasirox or any other ICT as prior chelation therapy. One patient (1.9%) died during the study. The cause of death was malignant melanoma with multiple metastasis in liver and spleen with unknown origin. Another contributing factor for death was liver failure and intrahepatic cholestasis. The event, death was not suspected to be treatment-related. A total of 13 patients (24.5%) had SAEs and no single SAE occurred in more than one patient. None of the SAEs were considered treatment-related. Adverse events leading to discontinuation of study treatment were reported in 4 patients (7.5%); one patient each had drug ineffective AE (1.9%) and serum ferritin abnormal AE (1.9%) considered to be treatment-related and led to discontinuation of study treatment.

Under AE of special interest grouping (>5% incidence), the special AE grouping term in which the majority patients had reported events was renal disorders (increased serum creatinine, acute renal failure, renal tubular disorder, acquired Fanconi's syndrome; 15 patients, 28.3%), mostly driven by urine protein-creatinine ratio increased (8 patients, 15.1%), proteinuria and blood creatinine increased (4 patients each PT, 7.5%). Under increased liver transaminases, hepatic failure, hepatitis (excluding infections) AE group term; hyper transaminasaemia PT was reported in 4 patients (7.5%). Increases in serum creatinine and liver function tests were observed in some patients, and those increases were consistent with the known safety profile of deferasirox FCT; worst post baseline elevations in serum creatinine of >ULN at 2 consecutive measurements at least 7 days apart occurred in 2 patients (3.8%).

Two patients (3.8%) had a worst post baseline ALT/SGPT level in the notable range (>5 times ULN and 2 times baseline value). Elevations of transaminases (AST/SGOT or ALT/SGPT) >10 times ULN were uncommon (1.9%); only one patient (1.9%) had a post baseline increase in AST/SGOT and ALT/SGPT values >10 times ULN and >2 times above baseline.

No patients had clinically significant ECG or ocular abnormalities. One patient had a clinically significant abnormality in audiometric examination at baseline and another patient had a clinically significant abnormality at baseline and during the study. Notable changes in systolic blood pressure (≤ 90 mmHg and decrease ≥ 20 mmHg; 4 patients, 7.5%) and diastolic blood pressure (≤ 50 mm of Hg and decrease ≥ 15 mmHg; 3 patients, 5.7%) values were observed in few patients and these values returned to normal in few days. Increase in body weight ≥ 7% was observed in 43 patients (81.1%).

In this study 66% of percent of patients (35 of 53) were female, and most of them (56.6%; 30 of 53) are of childbearing potential. Three patients reported positive urine test for pregnancy during the study, although women of child-bearing potential were informed (about unknown risks to the fetus if pregnancy were to occur during the study and need for adherence to the contraception requirement for the duration of the study) and trained when checked by site. Two of these were discontinued and another patient had spontaneous abortion. The event, spontaneous abortion was reported as an AE, moderate in severity and not treatment related. The study drug dosage was temporarily interrupted due to the event, spontaneous abortion.

Pediatric patients

All 3 pediatric patients experienced at least one AE which were mild to moderate in severity. All AEs were resolved except two AEs (Patient ITA-1276-00005: Asthenia [mild], Patient ITA-1276-00011: serum ferritin abnormal [moderate]) which were ongoing at the time of last reporting. None of the AEs were considered as related to the study drug except serum ferritin increased by ITA-1276-00008 and serum ferritin abnormal experienced by Patient -ITA-1276-00011. The most common AEs experienced by all pediatric patients were

asthenia and pharyngitis. None of the pediatric patients experienced any serious adverse event (SAE) or died during the study. In a single patient (Patient ITA-1276-00011), study treatment was discontinued permanently due to AE serum ferritin abnormal.

None of the pediatric patients had clinically significant abnormalities observed for laboratory parameters, electrocardiogram (ECG) parameters, audiometric, and ocular examination. All pediatric patients had notable ≥7% increase in weight (Week 2 to Month 26) (assessment was not done at Months 6, 8, and 25) for Patient ITA-1276-00005, Month 5 to Month 8 for Patient ITA-1276-00008, and Month 11 to Month 16 for Patient ITA-1276-00011).

In this study, Patient ITA-1276-00005 received 74 units of packed RBC, with the total volume of blood transfused being 18685 mL; Patient ITA-1276-00008 received 129 units of packed RBC, with the total volume of blood transfused being 33151 mL and Patient ITA-1276-00011 received 40 units of packed RBC, with the total volume of blood transfused being 9114 mL.

None of the reported AEs was considered suspected except serum ferritin increased by ITA-1276-00008 and serum ferritin abnormal experienced by Patient ITA-1276-00011.

No changes to the pediatric information of the current deferasirox Core Data Sheet (CDS) 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. The benefit-risk assessment for deferasirox is considered to remain positive for the currently approved indications in pediatric and in overall population.

CHMP comment:

The primary safety objective of the study was to evaluate the overall safety of deferasirox film-coated tablet (FCT) formulation in patients with transfusion dependent thalassemia or myelodysplastic syndrome (MDS).
A total of 53 patients were enrolled in the present study, of those 3 patients (5.7%) were under the age of 18 years (13, 15 and 16 years respectively) and 50 patients (94.3%) were aged ≥ 18 years. All the 3 patients aged <18 years had thalassemia as their main underlying disease.

Almost all patients (98.1%) reported at least one adverse event. The majority (>30%) of patients had AEs in the infections and infestations SOC (75.5%), gastrointestinal disorders SOC (67.9%), general disorders and administration site conditions SOC (45.3%), respiratory, thoracic and mediastinal disorders SOC (37.7%), investigations, musculoskeletal and connective tissue disorders (32.1% each SOC) and nervous system disorders SOC (30.2%).
One patient (72 years) with MDS died during the study.

Pediatric cases

Case 1 was about a 16-years-old male patient (ITA/1276_00005) who developed nausea, 2 episodes of moderate cough, pharyngitis (low grade), moderate chickenpox, rhinitis (low grade), asthenia (low grade), moderate fever, diarrhea and catarrhal rhinitis (low grade for both AEs). Study drug was pursued and the patient recovered from all AEs but Asthenia.

Case 2 was about a 15-years-old female patient (ITA/1276_00008) who developed multiple episodes of osteomuscular pain (low grade), multiple episodes of heart burn (low grade), irregular menstrual cycle,

moderate or low grade headaches, shoulder pain, 2 episodes of gastritis (low grade), moderate increase in serum ferritin, inferior lumbar pain, stye, asthenia, vertigo, inferior limb pain [musculoskeletal and connective tissue disorders], moderate flu like syndrome, mucositis of upper respiratory trast, palpitations, abdominal pain and left ipocondrium pain. Study drug was pursued and the patient recovered from all AEs.

Case 3 was about a 13-years-old male patient (ITA-1276-00011) who developed transaminasemia, moderate insufficient control of the ferritin value, headache, asthenia and moderate pharyngitis. Study drug was discontinued permanently due to serum ferritin abnormalities.

With a majority of patients ⩾ 18 years (94.3%) and only 3 (5.7%) pediatric patients, it is hard to draw any conclusion regarding the safety profile of deferasirox in both indications (transfusion dependent thalassemia or myelodysplastic syndrome (MDS)) based on data provided from this study. However, information from the 3 pediatric cases are in line with the known safety profile of Exjade.

Overall, this interventional study does not bring any new relevant information on safety of deferasirox.

3. Overall conclusion

The CICL670AIC04 study was an interventional study to collect additional data on safety and efficacy of Exjade® (deferasirox) film coated tablet (FCT) formulation in patients with transfusion dependent thalassemia or myelodysplastic syndrome (MDS) (very low, low or intermediate risk) when treated over 24 weeks in CICL670F2201 study.

With a majority of patients ≥ 18 years (94.3%) and only 3 (5.7%) pediatric patients, it is hard to draw any conclusion regarding the efficacy and safety profile of deferasirox in both indications (transfusion dependent thalassemia or myelodysplastic syndrome (MDS)) based on data provided from this study. Information from the 3 pediatric cases are in line with the known safety profile of Exjade.

Overall, this interventional study does not bring any new relevant information on safety and efficacy of deferasirox. No changes to the pediatric information of the current deferasirox Core Data Sheet (CDS) 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. The benefit-risk assessment for deferasirox is considered to remain positive for the currently approved indications in pediatric and in overall population.

☒ **PAM fulfilled (all commitments fulfilled) - No further action required**