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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/P46/076

## Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
**Telephone** +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
**Send a question via our website** www.ema.europa.eu/contact

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# 1. Introduction

On 30 April 2018, the MAH submitted a completed paediatric study for deferasirox, 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 study CICL670AGR04, 'CONVENIENCE: A multiCenter, nOn iNterVENtional study to evaluate the Impact of defErasirox on the quality of life of patients with beta thalassemia or sickle cell disease and transfusion - induCEd iron overload' is a stand-alone study.

## *2.2. Information on the pharmaceutical formulation used in the study*

The non-interventional nature of the study implies use of the commercially available form of deferasirox. The study was conducted with DFX DT (dispersible tablets) as the study drug. In September of 2017 DFX DT was substituted commercially with DFX FCT (film coated tablets). The results from the ECLIPSE trial showed a superiority of FCT vs DT in QoL-related parameters. To avoid any introduction of systematic positive bias any patients enrolled who switched to FCT were withdrawn from the study. Therefore, all collected and analyzed data refer to DFX DT.

## *2.3. Clinical aspects*

### 2.3.1. Introduction : Rationale and background

Adherence to iron chelation therapy is fundamental in transfusion-dependent patients, such as those with β-thalassemia and other transfusion-dependent forms of anemia requiring lifelong iron chelation therapy from early childhood, so that complications associated with transfusional iron overload are prevented. Furthermore, the extensive medical care required in these chronic, progressive and, if-unchelated, life-threatening conditions may impact the physical, psychosocial well-being and quality of Life (QoL) of patients and their families (Atkin 2001). Although QoL has emerged as a fundamental focus of comprehensive healthcare in this population, there is limited published data regarding the health-related QoL in patients with transfusion-induced iron overload and until recently no specific questionnaire was available for the assessment of the QoL of thalassemia patients. In view of this important need, the first Greek version of thalassemia-specific QoL questionnaire

[Self-administered Specific Thalassemia Quality of life instrument (STQOLI)] has been recently developed and validated (Lyrakos 2011[1]). Furthermore, the availability of iron chelators such as deferasirox (DFX) that, due to its pharmacological properties and its balanced efficacy and safety profile along with its once-daily convenient dosing regimen contributes to actual patient compliance and increases the effectiveness of chelation therapy, is important in optimizing treatment outcomes and improving QoLof iron-overloaded transfusion-dependent patients.

[1] Lyrakos GN, Vini D, Aslani H, et al (2012) Psychometric properties of the Specific Thalassemia Quality of Life Instrument for adults. Patient Prefer Adherence;6:477-97.

## Study CICL670AGR04: Research question and objectives

This study was designed to assess the health-related QoL (HRQoL) of patients with beta thalassemia or sickle cell disease who had been receiving blood transfusions and iron chelation, using the STQOLI questionnaire, after switching to DFX monotherapy. Moreover, the study aimed to further enrich the existing data on the efficacy and tolerability profile of DFX, as well as to assess patient's compliance and satisfaction with treatment in a 'real world' clinical setting, among a representative population of patients with β-thalassemia or sickle cell disease and transfusion-induced iron overload in Greece.

## Methods

### *Objective(s)*

The primary objective of this study was to evaluate the impact of DFX monotherapy on the thalassemia-specific quality of life at six months after switching to DFX monotherapy in patients with transfusion-induced iron overload.

Secondary objectives included:

• The evaluation of the impact on the thalassemia-specific QoL at 12 and 24 months after switching to DFX monotherapy in patients with transfusion-induced overload.

• The evaluation of the impact on the general QoL after switching to DFX monotherapy in patients with transfusion-induced iron overload.

• Assessment of the effectiveness profile of DFX treatment in the study population at the indicative study time points.

• Evaluation of the safety profile of DFX treatment under the setting of the standard clinical practice.

• Evaluation of patients' compliance with DFX treatment and reasons for non-compliance.

• Assessment of patient satisfaction with DFX therapy.

• Assessment of DFX tolerability.

### *Study design*

The design was that of prospective multicenter, non-interventional, observational, open-label, phase IV study. The study protocol and ICF were reviewed and approved by the Institutional Ethics Boards and the relevant financial agreements were executable, before initiation of the study at any participating site.

The study has been designed to assess the HRQoL of patients with beta-thalassemia or sickle cell disease who are receiving blood transfusions and iron chelation with DFX, using the STQOLI questionnaire. A power of approximately 80% was considered adequate for the assessment of 150 patients in order to answer the research question; the difference in total STQOLI score at 6 months of therapy from prior DFX therapy commencement. Hence, the hypothesis of a 3-point mean change in STQOLI total score along with the aforementioned power of the study confirmed the strength of the study design. Data required to address study specific objectives were collected from patients' hospital files. A Novartis representative reviewed the protocol and the case report form (CRF) with the physicians and the staff involved in the study. Physicians were requested to monitor patients for a planned observation period of up to 24 months under which patients continued to receive DFX treatment according to the approved product's labelling.

This clinical study was conducted in 16 investigational sites throughout Greece; one site did not enroll any patients. Physicians were requested to monitor patients for a planned observation period of

24 months under which patients continued to receive DFX treatment according to the approved product's labeling. Four follow-up visits (6, 12, 18 and 24 months after treatment with DFX initiation) were scheduled during the observation period. Overall 80 patients were screened and 68 patients were enrolled. One of the enrolled patients was pediatric (18>age>14 y)

***Study population /Sample size***

One hundred and fifty (150) patients with beta-thalassemia or sickle cell disease and transfusion-induced iron overload were planned to participate in the study according to the inclusion and exclusion criteria.

Overall 80 patients were screened and 68 patients were enrolled. One of the enrolled patients was pediatric (18>age>14 y).

| |
|---|
| *CHMP comment:* |
| Only one paediatric patient was enrolled. |

***Treatments***

DFX monotherapy, dispersible tablets

***Outcomes/endpoints***

The primary endpoint of this observational study was the change in STQOLI score at 6 months of DFX treatment when compared to the score before the switch to DFX.

The study secondary endpoints included the following:

- Change in STQOLI score at 12 and 24 months of DFX treatment, when compared to the score before the switch to DFX.
- Change in the EQ-5D VAS and index scores at 6, 12 and 24 months of DFX treatment, when compared to from the ones before the switch to DFX.
- Change in cardiac iron overload, measured by MRI T2* values as performed in clinical practice, after 12 and 24 months of DFX treatment, when compared to the values before the switch to DFX.
- Change in liver iron concentration (LIC) measured by liver MRI T2* technique as performed in clinical practice, after 12 and24 months of DFX treatment, when compared to that before the DFX.
- Change in serum ferritin levels, as measured in clinical practice, after 6, 12, 18 and 24 months of DFX treatment, when compared to those before the switch to DFX.
- Proportions of patients who experience adverse events (AEs), serious adverse events (SAEs), adverse drug reactions (ADRs) and serious adverse drug reactions (SADRs) (including both clinical and laboratory abnormalities).
- Proportion of enrolled patients reporting 'excellent/very good compliance with DFX therapy', via a 5-point Likert scale.
- Frequency of patient-reported reasons for poor compliance after 6, 12, 18 and 24 months of DFX monotherapy.

- Proportion of patients reporting 'satisfied/very satisfied with DFX treatment', via a 5-point Likert scale after 6, 12 and 24 months of DFX treatment.

***Statistical Methods***

Statistical analysis was performed:

• In the Intention to Treat (ITT) set which consists of all eligible patients who will be enrolled in the study regardless of whether or not they will finally complete the study;

• In the Per Protocol Set (PPS) which consists of all eligible patients from ITT who will complete the study, i.e., the 24-month follow-up period and;

• In subsets of ITT with available data at each indicative timepoint (visit).

In principle, the analyses of baseline characteristics as well as of safety data were based on ITT, whereas the changes in efficacy variables as well as in STQOLI and EQ-5D at the different time points of the study were calculated using the subsets of ITT with available data at each indicative timepoint.

Patients who were erroneously enrolled in the study (i.e., not fulfilling the eligibility criteria) were excluded from all analyses of this study and any violations of the protocol were reported in detail in the clinical study report (CSR)

## Results

**The main study results are:**

- QoL did not show any statistical significant changes from baseline in STQOLI at 6 months (primary endpoint). With respect to other timepoints, STQOLI had a slight trend to decrease, whereas EQ-5D index score showed a slight increase at 6 and 12 months from baseline, that was not sustained at EOS. EQ-5D VAS scores describing patients' health state increased throughout the study; the increase was statistically significant at 12 months.

- Liver iron overload showed a trend to decrease throughout the study, as LIC decreased at the end of study (EOS) compared to baseline, although these changes did not reach statistical significance. Serum ferritin levels and LVEF remained practically unchanged.

- Compliance with treatment and satisfaction with DFX was increased throughout the study, although the increase was not statistically significant.

- The most common reason for patients' non-compliance was patients' negligence.

- AEs were reported in 80.9% of the study's patients. In total and irrespective of the causality assessment, SAEs occurred in 36.8%.

- Of the SAEs of the present study, 14.9% were suspected to be related to the study drug.

- The most common ADRs encountered were increased serum creatinine, abdominal pain, albuminuria/microalbuminuria/proteinuria, and increased liver transaminases.

- There was one instance reported of each of the following AEs, whose frequency is otherwise not known in the product's SmPC and should be noted: neutropenia, thrombocytopenia, alopecia, and allergic dermatitis (hypersensitivity).

- No deaths were documented throughout the study duration.

- Patients who withdrew from DFX treatment due to an AE were 26.5% of the study population.

•.The pediatric patient withdrew within 3 months due to an increase of serum creatinine levels, before the planned first assessments related to the objectives of this study.

*CHMP comment:*

No conclusions can be derived for the pediatric cohort of this study since the only one pediatric patient withdrew before the planned first assessments related to the objectives of this study.

***Efficacy results***

Two validated instruments were used for assessing the quality of life in this study – STQOLI and EQ-5D. For details of the instruments, refer to [StudyICL670AGR04-Section 10.4].

Quality of life (QoL) at baseline

At baseline, the STQOLI total score for the pediatric patient was 73.46, which was higher than the mean STQOLI total score of the overall study population (N=68, mean score: 63.69). The domain scores for disease and symptoms (90.27), psychosocial impact (71.66), and chelation therapy impact (82.05) was higher in the pediatric patient than the study population mean (61.86, 55.80, 57.87) but the transfusion impact (53.32) was lower than the study population mean (64.37) [Study ICL670AGR04-Section 10.4].

At baseline, EQ-5D VAS for the pediatric patient was 90 (high QoL, population mean: 77.29) and the EQ-5D index was 0.88 (population mean: 0.83). The patient reported some problems in usual activities and pain/discomfort dimension, no problems were reported in the other dimensions. The values of his cardiac magnetic resonance imaging (MRI) T2*, liver iron concentration (LIC), serum ferritin level and left ventricular ejection fraction at baseline were 23 msec, 3 mg Fe/g, 1400 µg/L and 58% respectively.

Change in QoL, iron overload parameters, compliance

Apart from the baseline QoL data, no other related data were collected for the pediatric patient as he withdrew from the study before the planned data collection at 6 months.

*CHMP comment:*

No conclusion can be drawn since only baseline QoL data were collected for the single pediatric patient.

***Safety results***

The pediatric patient experienced two AEs (summarized in Table 5-1):

- an increase in serum ferritin (non-serious AE, not evaluable)
- a non-serious adverse drug reaction of elevated blood creatinine resulting in permanent discontinuation of the study drug

**Table 5-1 Safety events in the pediatric patient**

| Preferred term/ System organ class | Seriousness | Severity | Period | Causality | Action taken | Outcome |
|---|---|---|---|---|---|---|
| Serum ferritin increased/ Investigations | Non-serious | - | 12-Apr-2016 - no end date listed | Not assessed | - | Unknown |

| Preferred term/ System organ class | Seriousness | Severity | Period | Causality | Action taken | Outcome |
|---|---|---|---|---|---|---|
| Blood creatinine increased/ Investigations | Non-serious (AE of special interest) | Mild | 22-Jun-2016 to 05-Jul-2016 | Related | Permanent discontinuation of Exjade | Recovered |

Source: [Study ICL670AGR04-Table 10-23].

During the time the pediatric patient was on study, only one hematological and biochemical examination was recorded. Outside of normal range values were recorded for hemoglobin (11.7g/dL), hematocrit (32.5%), RBC (4 × 10^6/µL), eosinophils (5.4%), total bilirubin (4.59mg/dL) and serum ferritin (1400 µg/L). All these values were considered clinically non-significant or related to the primary medical condition. The blood creatinine value was not provided.

*CHMP comment*:

The pediatric patient experienced two non-serious AEs (an increase in serum ferritin and elevated blood creatinine). This latter resulted in permanent discontinuation of the study drug and is already reported in the current label as a very common ADR.

### 2.3.2. Discussion on clinical aspects

The single pediatric patient enrolled withdrew within 3 months due to an increase of serum creatinine levels, before the planned first assessments related to the objectives of this study.

No efficacy conclusion can be derived from the single pediatric patient enrolled in this study, as only baseline data for this patient are available.

Regarding safety aspect, "Blood creatinine increased" that lead to discontinuation of the patient is already reported in the current label as a very common ADR.

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

The benefit-risk assessment for deferasirox is considered to remain positive for the currently approved indications in paediatric and in overall population.

## 3. CHMP overall conclusion and recommendation

☒ Fulfilled:

No changes to the paediatric 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 paediatric information in the EU SmPC

The benefit-risk assessment for deferasirox is considered to remain positive for the currently approved indications in paediatric and in overall population.