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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: EMEA/H/C/000670/P46/065

Note

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

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1. Introduction

On 30 September 2015, the MAH submitted one completed paediatric studies for Exjade (observational), 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 the study is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The registry is observational and does not impose a therapy protocol, diagnostic/therapeutic interventions or a strict visit schedule. Patients were treated with an oral iron chelator according to the investigator's judgment and in accordance with the local (country-specific) prescribing information. Data about all treatments applied to the patients were collected. Treatment included commercially available Exjade, which is brand name for deferasirox and is presented as dispersible tablets in 3 doses strengths: 125, 250 and 500mg..

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 (observational) and a clinical overview of this study.

The MAH submitted one final report for:

- CICL670ATR03 : A 3 year observational study (registry) of children with hemoglobinopathies at enrolment treated with oral iron chelators due to transfusional hemosiderosis.

2.3.2. Clinical study

CICL670ATR03 : A 3 year observational study (registry) of children with hemoglobinopathies at enrolment treated with oral iron chelators due to transfusional hemosiderosis.

Description

This is a prospective, multicentre non interventional observational registry in Turkey to collect data of patients aged from 2 to 18 years-old with hemoglobinopathies who are treated with oral iron chelators therapy for transfusional hemosiderosis. Patients were followed up for 3 years.

Methods

Objective(s)

Primary objectives:

Primary objectives of the present study are to study the magnitude of the problem of iron overload in Turkey, gaining insight about this condition and the patterns of care regarding the use of oral iron chelating therapy for transfusion-dependent hemoglobinopathies in this country.

Secondary objectives:

To describe the demographics of patients with hemoglobinopathies and iron overload management of these patients requiring chronic transfusional therapy

To investigate any correlation between secondary iron overload due to transfusions, treatments received and co-morbidities (including cardiac function)

Collect data on (if available)

- Adverse events
- Liver and kidney functions
- Auditory and ophthalmology assessments
- Growth and sexual development for pediatric patients
- To list transfusion requirements and the types of iron chelation therapy and regimens employed in Turkey

Study design

This study is a prospective, multi-center, non-interventional study in Turkey designed as a registry of patients 2 – 18 years of age with hemoglobinopathies, who are on oral iron chelator therapy at the time of enrollment with transfusional hemosiderosis. The study was initiated on 23 Nov 2010 (FPFV) and ended on 17 October 2014 (LPLV). The study was conducted in 31 sites in Turkey.

CHMP comment
This is an observational study which is not designed to assess the efficacy and safety of chelation therapy (in particular deferasirox) according to the MAH.

Study population /Sample size

All eligible patients in all centers in Turkey which are responsible in diagnosis and management of patients with hemoglobinopathies and agree to participate in the registry during the 1 year-recruitment period of the study, or until the target number of patients is achieved. The estimated sample size was **400 patients.**

Inclusion criteria

Eligible patients must meet all of the following criteria:

Written informed consent obtained from the patient and the child's legal guardian for children.

Male or female patients aged 2-18 years at enrollment.

Patients who have transfusion-dependent anemia, such as major β- thalassemia and sickle cell disease.

Patients who have an iron overload as defined in established patients management guidelines regarding oral iron chelation therapy as a cumulative blood transfusion history of ≥100 mL/kg of packed red blood cells (approximately 10 units for a 20 kg patient) and/or a serum ferritin consistently >1000 µg/L.

Patients beginning or under treatment with any oral iron chelator (under prescription) for transfusional hemosiderosis at the time of enrollment.

Exclusion criteria

Patients with any of the following will NOT be included in the study:

Patients who have any contraindication for treatment with any iron chelator according to the local prescribing information

Patients with non-transfusional hemosiderosis.

Unwilling or unable to comply with the protocol.

Severe concomitant illnesses that might make the completion of the registry unlikely (e.g. cancer, active AIDS).

Patients involved in another clinical trial.

Pregnancy or breastfeeding

Known sensitivity to class of oral iron chelators

Use of any investigational agent in the last 30 days

Treatments

The study protocol does not impose a therapy protocol or diagnostic/therapeutic interventions. Patient will be treated with an oral iron chelator according to the investigator's judgment and in accordance with the local (country-specific) prescribing information.

Outcomes / endpoints

Statistical Methods

Investigators will enter the information required by the protocol into the Novartis Case Report Forms (CRFs). Non-obvious errors or omissions will be entered on Data Query Forms, which will be returned to the investigational site for resolution.

The data from all centers will be pooled and summarized with respect to demographic and baseline characteristics and efficacy and safety observations. Data will be presented for the complete intent-to-treat population as well as the per-protocol population (all patients who completed the study without major protocol deviations).

A multivariate Cox proportional hazards regression model will be applied to correlate secondary iron overload (ferritin levels) due to transfusions and treatments received to comorbidities .

For the assessment of safety based on the frequency of serious adverse events; serious adverse events will be summarized by presenting for each treatment group the number and percentage of patients having any serious adverse event, having a serious adverse event in each body system and having each individual serious event. Any other information collected (e.g. severity or relatedness to study medication) will be listed as appropriate.

Results

Recruitment / Number analysed

A total of 483 paediatric patients (aged 2-18 years) were enrolled: 459 patients (95%) were diagnosed with beta-thalassemia major and 24 (5%) had sickle cell anaemia. A total of 347 patients completed the study and were followed during 3 years. A total of 136 patients discontinued from the study. The mean age of the patients was 9.38±4.10 years. The distribution of patients according to age groups was as followed: 143 patients (29.6%) aged 2-6 years, 223 patients (46.2%) aged 7-12 years, 117 patients (24.2%) aged 13-18 years

Baseline data

At baseline, 90.4% (n=415) of the patients with beta-thalassemia major were receiving DFX, 7.6% (n=35) of the patients were receiving deferiprone (DFP) and 2 % (n=9) were treated with deferoxamine (DFO).

The mean daily doses of DFX and DFP were 26.37±6.13 mg/kg/body weight and 69.59±17.17 mg/kg/body weight respectively while DFO mean dose was 60.83±21.08 mg/kg/body weight. All patients with sickle cell anaemia (n=24) were receiving DFX, and the mean daily dose of DFX was 25.15±5.41 mg/kg/body weight

Within the total population, 71 patients (14.7%) presented with concomitant diseases at baseline and the most common concomitant diseases were endocrine dysfunction, cardiac insufficiency and liver disease. Of those 71 patients, 65 (14.8%) were receiving DFX and the endocrine dysfunction (29 patients, 6.6%) was the most common concomitant disease. Within endocrine complications, hypothyroidism was the most frequent 8 (27.6%) followed by osteoporosis 5 (17.5%)

Within the study, 5 patients were reported to be positive for HBsAg suggesting an ongoing infection of hepatitis B. All of these reported positive HBsAg assessments were reported for patients receiving DFX. The presence of anti-HBc was reported in 13 patients throughout the study,

indicating previous or ongoing infection with HBV in an undefined time frame. Eight patients of those were receiving DFX.

A considerable number of assessments were positive for anti-HBs. The presence of anti-HBs is generally interpreted as indicating recovery and immunity from HBV infection. Anti-HBs also develop in a person who has been successfully vaccinated against hepatitis B.

Furthermore, there were 8 patients tested positive for Anti HCV within the study, potentially suggesting the presence of hepatitis C infection. All of them were reported for patients receiving DFX

Efficacy results

Efficacy was assessed with SF change from baseline to end of study. SF data of all evaluable patients in this study demonstrated that SF levels decreased from mean 2056.56 ng/dl to 1636.70 ng/dl in DFX treated patients.

In this study, T2* MRI was used to detect cardiac iron deposition and was suggested at baseline, after 2 years of observation and after 3 years at end of study. T2* MRI was performed at baseline in 68 patients of whom 62 were treated with DFX. Of those, 43 (69.4%) patients had T2* >20 ms. One patient treated with DFX had T2* <5 ms at baseline. After 2 years, 40 DFX patients were assessed with T2* MRI and 28 (84.8%) of those patients had normal results (T2* >20ms). Two patients receiving DFX had 5>T2*<10. At the study end, 27 DFX patients of total 37 were evaluated for cardiac T2*. Five (20.8%) patients had T2* between 10 to 20 ms which is regarded as moderate cardiac IOL. Importantly, 19 (79.2%) patients who were receiving DFX presented with T2* greater than 20 ms at the last visit. Overall, majority of the patients treated DFX at all three visit had T2* above 20 ms. The study's design and the manner in which data was collected does not allow one to make a conclusion on cardiac efficacy. The T2* results are presented over time but rather at each visit without a possibility to relay them to previous or subsequent visits' results.

Liver assessment by MRI for IOL was suggested to be completed at the same frequency as T2* MRI at baseline, after 2 years and after 3 years at end of study. The results were referred to "normal" or "abnormal" based on judgment of the physicians. Notably, both categories were not explicitly defined. At baseline, liver MRI was performed in 66 patients of whom 62 were treated with DFX. A total of 19 (30.6%) DFX patients had a normal assessment. After 2 years, 51 patients treated with DFX were evaluated for IOL in liver, of whom 36 (70.6%) were assessed as normal. At the study end, 26 (66.7%) of 39 DFX patients, had a normal MRI assessment as reported by the investigators.

The study's design and the manner in which data was collected do not allow one to make a conclusion on liver efficacy. The LIC results are collected in a numerical way and were not presented over time but rather at each visit without a possibility to relay them to previous or subsequent visits' results.

CHMP comment

No specific analyses of the efficacy in pediatric patients have been conducted. This is a prospective, multicenter and observational study thus non-randomized and non-controlled with main limitations including potential selection bias, missing data.

At baseline, 415 patients with beta-thalassemia major and 24 patients with sickle cell anemia received DFX. The mean daily doses of DFX used in both population were usual (recommended doses: 20-30 mg/kg/body weight).

Reduction in mean SF was reported for all evaluable DFX treated patients from BL of 2056.6 ng/ml to 1636.7 ng/ml at 3 years.

Change in cardiac overload measured by MRI T2* was provided but the study design cannot allow to conclude on cardiac efficacy.

T2* MRI was performed at baseline in 62 of 68 DFX patients. 43 (69.4%) patients present moderate cardiac overload (T2*>20 ms) and one patient treated for a severe cardiac overload (T2*<5). After 2 years, T2* MRI was performed in 40 DFX patients. 28 (84.8%) had normal results (T2* >20ms). Two patients receiving DFX had 5> T2*<10. After 3 years, T2* MRI was performed in 27 of 37 DFX patients 19 (79.2%) patients presented T2* > 20 ms. Five (20.8%) patients had T2* between 10 to 20 ms.

Thus, majority of the T2* MRI evaluable DFX treated patients at all three visit had T2* > 20 ms. This observational study provide long-term efficacy T2* results but without possibility to relay them to previous or subsequent visits' results.

In the same way, percentage of "normal" hepatic T2* MRI (result judged by physicians) increases in evaluable DFX treated patients after 2 and 3 years compared to baseline but there's no possibility to link the results between each visit and thus to conclude to efficacy of DFX on liver iron overload.

Safety results

Of the 483 patients enrolled, 30 (6%) discontinued chelation therapy due to serious adverse events (SAEs), 29 patients of those were receiving DFX. The most frequently reported SAE was bone marrow transplant and stem cell transplant patients who discontinued the study (Hospitalization for an elective procedure was wrongly defined as SAEs).

Three patients discontinued chelation therapy due to administration of intensive chemotherapy. **2 patients died** during the observational period (see below). Of 101 patients who the primary reasons for withdrawal was "other", majority 66 (65.3%) withdrew due to lost to follow up.

Within the total population, there were 159 (32.9%) patients who experienced adverse events (AEs). Most of the AEs were allogeneic bone marrow transplantation therapy 25 (5.2%), followed by endocrine 10 (2.1%) and osteoporosis 10 (2.1%). Of note, allogenic bone marrow transplantation is an elective procedure and is generally not reported as AE.

A total of 143 (32.6%) patients of 439 treated with DFX experienced AEs within the study.

The most commonly AEs were allogeneic bone marrow transplantation therapy 24 (5.5%), osteoporosis 10 (2.3%) followed by endocrine 9 (2.1%) and cough 9 (2.1%).

For other two chelators, AEs were reported in 4 (44.4%) patients out of 9 treated with DFO, and 12 (34.3%) patients out of 35 who were receiving DFP.

Fatal cases:

Two deaths were reported during the study. A 15 years old female patient with beta thalassemia treated with DFX died due to upper gastrointestinal bleeding caused by esophageal variceal. As assessed by the investigator, the event was not suspected to be related to DFX. The cause of death for the other beta thalassemic patient, female 18 years of age, was cardiac insufficiency and cardiogenic shock. This patient was diagnosed with cardiac insufficiency 2 years ago and was receiving Digoxin (1x1) and captopril (1x1). At the time of the event the patient was treated with

DFP and DFO and the investigator did not suspect a relationship between the event and DFP/DFO combination therapy.

SAEs, irrespective of relationship to DFX treatment, were reported in 60 (13.7%) DFX patients. Majority of SAEs were the allogeneic bone marrow transplantation therapy 24 (5.5%) and stem cell transplantation 7 (1.6%) and were not suspected to be related to DFX. Of note, those are elective procedures and are generally not reported as SAEs.

Only 2 patients experienced SAEs, both of which were suspected by investigators to be related to DFX treatment:

☐ One patient experienced a *hepatic enzyme increase* at two different time points; both events resolved with dose adjustment.

☐ The other patient presented with *kidney tubule disorder and abdominal pain*. DFX was permanently discontinued and both events were resolved.

A total of 403 DFX patients had serum creatinine (SCr) evaluated at baseline with mean 0.41 mg/dl. At the study end, the mean SCr was 0.47 mg/dl , remaining stable over the duration of the study. At baseline, the mean creatinine clearance (CrCl) was 180.9 ml/min for 383 evaluable patients who were treated with DFX. These rather high CrCl values remain consistent throughout the study and a mean of 179.9 ml/min was reported at the study end.

A total of 394 DFX patients had ALT evaluated at baseline. The mean alanine aminotransferase (ALT) has gradually decreased overtime from 35.0 U/L at baseline to 23.57 U/L at the study end, remaining within a normal range. Overall, approximately 80% of patients treated with DFX who underwent assessment within the study had a normal sexual development as defined by the investigators. In general, the proportion of patients with a delayed sexual maturation throughout the study remained unchanged ranging between 14.5% to 21.3%.

Importantly to highlight that 31 (14.5%) patient receiving DFX at baseline entered the study with a delayed sexual assessment and 9 of those were assessed by the investigators as normal at the study end. Conversely, some patients showed change from normal to abnormal within the study.

Audiometry and ophthalmology assessments were suggested at baseline (visit 1), after 2 years of observation (visit 5) and after 3 years at the end of the study (visit 7).Within the study, a normal hearing assessment was observed in approximately 93% of patients treated with DFX. There were patients who demonstrated hearing abnormalities at one or more of the three visits: eight patients (3.5%) at visit 1, 7 patients (4.9%) at visit 5 and 6 (4 new and 2 previously reported after 2 years) patients (6.5%) at visit 7. Most common abnormalities were hearing loss. No causality assessment was reported by the investigators. Below is the summary of patients who demonstrated hearing abnormalities at study visits.

Of these 8 patients with hearing abnormalities at visit 1 (baseline), the assessment for 7 patients were either not performed or not reported by the investigators at visit 5 and visit 7; and 1 patient who had mild conductive hearing loss on right ear due to effusion at visit 1 was reported by the investigator as normal at visit 5. Of the 7 patients who reported hearing abnormalities at visit 5, 3 patients were assessed as normal at visit 1 and the visit 1 assessment was unknown for the other 4 patients

At visit 7, 2 patients of the 6 had abnormal hearing at visit 5. The other 4 patients had a normal hearing at visit 5. Overall, total of 19 patients were reported with audiometry abnormalities within the study. Of those 19, eight patients had abnormal assessments at baseline and one of them was assessed as normal at the visit 5. New hearing abnormalities were observed in 7 patients who were

assessed with normal audiometry at previous visits. The baseline assessment for the remaining 4 patients who presented with abnormal hearing assessment was either not performed or not reported by the investigators thus one cannot conclude if those were new or existing abnormalities.

Ocular evaluation was reported by investigators as normal in greater than 99% of DFX patients who underwent ophthalmic examination throughout the study. Only 1 (0.5%) patients within the study had fundus abnormalities as assessed by the investigators. No ocular abnormalities were observed at the end of the study in patient treated with DFX

CHMP comment

As a general comment, the safety assessment in paediatric population in this study was not the primary objective of this study ATR03. Only descriptive data were recorded.

In this observational study, all patients did not receive Exjade but a vast majority (439/483) received an iron chelator therapy including Exjade. The collection of safety data was part of the secondary objective of this study. This study enrolled 483 paediatric patients (459 beta-thalassemic patients and 24 with SCD) and finally 347 patients completed the study and were followed during 3 years.

Among the 483 paediatric patients, 433 received monotherapy (85% Exjade, 3.5% Ferriprox and 1% Desferal) and 55 received iron chelators combinations (4% each: Exjade+ Desferal and Exjade+ Ferriprox ; 1% Ferriprox+Desferal and 2.3% Exjade+Desferal+ferriprox).

Currently, Exjade is contraindicated with other iron chelators in Europe as the safety of such combinations has not been established. Therefore, a thorough safety review of all patients with iron chelators combinations containing Exjade in this observational study would be useful to describe the safety profile of such combinations in real life, especially in those paediatric patients (beta-thalassemic and SCD). Also the MAH should try to analyse the reasons why prescribers used such combinations (in therapeutic strategy).

During this study, 2 fatal cases were reported :

1) one GI haemorrhage in a 16 years-old female patient (beta-thalassemic). This case was already reported in the previous PSUR 14 . The MAH claims that this GI haemorrhage is not related to Exjade as it occurred in a context of oesophageal variceal). However, in CIOMS form (in EV) no information on pre-existing or concomitant oesophageal lesions is mentioned. Therefore, the role of Exjade cannot be ruled out. The MAH should clarify.

2) one cardiac insufficiency and cardiogenic shock in a 18 years-old female patient (beta-thalassemic) under the combination of DFP and DFO. No more information are available in the clinical safety report.

A total of 143 AEs were reported under Exjade therapy: mainly are allogenic bone marrow transplantation (25), osteoporosis (10 *or 11?? in table 103*) and endocrine disorders 9 *or 10 ?? in table 103* / cough (9). Also hepatic disorders were also reported (10).

Hearing abnormalities did occur among paediatric patients with long term DFX treatment (7 patients (/439 ; 1.6%) have reported newly occurring hearing abnormalities which should be adequately follow.

Also at the end of study, delayed sexual development was reported in both genders within 2 age-group: 7-12 years-old and 13-18 years-old. We agree that these data should be taken with caution as we cannot exclude the role of previous chelation therapy (DFO) as 2/3 of patients with Exjade were previously treated with DFO and the role of underlying disease. Also the assessment by the

Tanner staging (a standard methodology to evaluate sexual maturation) was not performed in this study. However, these finding should be kept in mind as they are not consistent with the previous analyses of study 107E1 (follow-up of 5 years of beta-thalassemic patients).

In this clinical study report of study ATR03, a lot of **discrepancies** have been noted:

1) the cross references for tables in the clinical expert overview are not consistent with the tables in the clinical study report leading to misinterpretation of data (*e;g : cross reference to table 156 page 8 of the overview while no table 156 is included in the clinical study report*).

2) Discrepancies between the table untitled "treatment with iron chelators" which described action taken with iron chelators therapy and the reason to stop treatment and the table untitled "adverse events" which listed all adverse events (serious and not serious) by patient with grade, action taken and relationship with study drug.

For instance, some adverse events considered as the reason for treatment interruption in the table "treatment with iron chelator" are not reported as adverse events in the table "adverse events". The main AEs with Exjade which are not listed in the table "adverse events" are *ALT and AST increased* (patient 04-04 ; 08-28; 14-16; 14-23; 15-01; 19-24; 27-02; 45-09; 45-13;…) , renal disorders (*tubulopathy,* 21-16; UPCR: 0.93, 29-31; creatinine increased, 36-04), and *neutropenia* (15-14), *allergic rash* (08-11), LDH increased (18-01), EBV infection (41-09), influenza (46.02).

Therefore the data provided contain too many discrepancies to make a correct assessment. No clear conclusion can be drawn from these erroneous descriptive data.

Even if the study contains only descriptive safety data, the MAH is requested to provide a correct comprehensive safety analysis of this study (for SAE and non SAE occurring during therapy including Exjade) with analysis of time to onset, circumstances of occurrence, potential risk factors, predisposal factor, dechallenge/rechallenge, outcome, action taken with the product. Also, an additional review of events of interest (such as renal, hepatic disorders, hearing abnormalities, long term events (related to time exposure) … to name a few) in this paediatric population should be provided.

MAH's conclusion

The data collected in this paediatric registry are consistent with the efficacy of DFX in reducing IOL in both the paediatric and adult patients. Overall, there were no unexpected safety findings in pediatric patients following long-term treatment with DFX. Importantly, no clinically significant changes in liver or kidney function in the patients receiving DFX. The safety profile for the paediatric patients remains consistent with the known profile of DFX. Data collected on sexual development by physical examination are not conclusive; Tanner staging, a standard methodology for assessment of sexual development, was not mandated by the study protocol and were not collected.

In conclusion, the benefit to risk relationship for DFX 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 Exjade (deferasirox) Core Data Sheet are proposed as a result of this registry due to the limitations of the data collected in particular on sexual development, and no regulatory consequences of the submitted study are anticipated for the pediatric information in the EU SPC.

CHMP comment

Efficacy

In conclusion, no specific analyses of the efficacy in pediatric patients have been conducted.

Reduction in mean SF, improvement of cardiac (T2* > 20 ms) parameters relative to cardiac iron overload was observed for evaluable DFX treated patients at 3 years. However, the study design cannot allow to conclude on efficacy of DFX on cardiac iron overload. Concerning liver assessment, the data do not allow to make conclusion on liver efficacy.

Safety

This descriptive study is particularly of interest because there is a follow-up of these paediatric patients during 3 years (long term exposure). Delayed sexual development was reported in both genders within 2 age-groups : 7-12 years-old and 13-18 years-old. Even if we take into account limitation of data collected (Tanner staging not performed), we consider that these finding should be kept in mind as they are not consistent with the previous analyses of study 107E1 (follow-up of 5 years of beta-thalassemic patients).

Based on the data provided in this descriptive study, **we cannot draw any conclusion on the safety profile of paediatric patients included in this study** and treated by Exjade (in monotherapy or in combination).

Indeed, **too many discrepancies have been identified to correctly assess the safety data recorded in this study**. Therefore, the MAH is requested to provide a correct comprehensive safety analysis of this study (for SAE and non SAE occurring during therapy including Exjade) with analysis of time to onset, circumstances of occurrence, potential risk factors, predisposal factor, dechallenge/rechallenge, outcome, action taken with the product…). Also, an additional review of events of interest (such as renal, hepatic disorders, hearing abnormalities, long term events (related to time exposure) … to name a few) in this paediatric population should be provided.

Also, Exjade is currently contraindicated with other iron chelators in Europe as the safety of such combinations has not been established. Therefore, a thorough safety review of all patients with iron chelators combinations containing Exjade in this observational study would be useful to describe the safety profile of such combinations in real life, especially in those paediatric patients (beta-thalassemic and SCD). Also the MAH should try to analyse the reasons why prescribers used such combinations (in therapeutic strategy).

Particularly, the MAH should clarify in the fatal GI haemorrhage case occurring in a 16 years-old female patient how the MAH has the information that “GI haemorrhage is not related to Exjade as it occurred in a context of oesophageal variceal” while in CIOMs form of the case in EV, no such information is recorded.

2.3.3. Discussion on clinical aspects

Efficacy

As a general comment, efficacy conclusions are difficult to drawn since efficacy of deferasirox is not a primary objective of these both observational studies. Only descriptive data are available.

In the study ATR03, reduction in mean SF, improvement of cardiac (T2* > 20 ms) parameters relative to cardiac iron overload was observed for DFX treated patients with b-TM or SCD at 3 years. However, the study design cannot allow to conclude on efficacy of DFX on cardiac and liver iron overload.

Safety

As a general comment, safety conclusions are difficult to drawn since safety of deferasirox in paediatric population is not a primary objective of these both observational studies. Only descriptive data are available.

In the study ATR03, a vast majority of patients enrolled in this registry in Turkey (439/483) received an iron chelator therapy including Exjade. The collection of safety data was part of the secondary objective of this study. This descriptive study is particularly of interest because there is a follow-up of these paediatric patients during 3 years (long term exposure**). Delayed sexual development was reported in both genders within 2 age-groups : 7-12 years-old and 13-18 years-old.** Even if we take into account limitation of data collected (Tanner staging not performed), we consider that these finding should be kept in mind as they are not consistent with the previous analyses of study 107E1 (follow-up of 5 years of beta-thalassemic patients).

Based on the data provided in this descriptive study, we cannot draw any conclusion on the safety profile of paediatric patients included in this study and treated by Exjade (in monotherapy or in combination). Too many discrepancies have been identified to correctly assess the safety data recorded in this study.

3. CHMP overall conclusion and recommendation

Efficacy

As a general comment, efficacy conclusions are difficult to drawn since efficacy of deferasirox is not a primary objective of this observational study. Only descriptive data are available.

In the study ATR03, reduction in mean SF, improvement of cardiac (T2* > 20 ms) parameters relative to cardiac iron overload was observed for DFX treated patients with b-TM or SCD at 3 years. However, the study design cannot allow to conclude on efficacy of DFX on cardiac and liver iron overload.

Safety

As a general comment, safety conclusions are difficult to drawn since safety of deferasirox in paediatric population is not a primary objective of this observational study. Only descriptive data are available.

In the study ATR03 (transfusion dependant hemoglobinopathies : beta thalassemic/SCD population), delayed sexual development was reported in both genders within 2 age-groups : 7-12

years-old and 13-18 years-old. Even if we take into account limitation of data collected (Tanner staging not performed), we consider that these finding should be kept in mind as they are not consistent with the previous analyses of study 107E1 (follow-up of 5 years of beta-thalassemic patients). Also, we cannot draw any conclusion on the safety profile of paediatric patients included in this study and treated by Exjade (in monotherapy or in combination) : too many discrepancies have been identified to correctly assess the safety data recorded in this study.

☐ **Fulfilled:**

☒ **Not fulfilled:**

Based on the data submitted, the MAH should provide description of the additional clarifications requested per study as part of this procedure. (see section "Additional clarification requested")

4. Additional clarification requested

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

Study ATR03

1- Too many discrepancies have been identified to correctly assess the safety data recorded in this study ATR03. Therefore, the MAH is requested to provide a **correct comprehensive safety analysis** of this study (for SAE and non SAE occurring during therapy including Exjade) with analysis of time to onset, circumstances of occurrence, potential risk factors, predisposal factor, dechallenge/rechallenge, outcome, action taken with the product…). Also, an **additional review of events of interest** (such as renal, hepatic disorders, hearing abnormalities, long term events (related to time exposure) … to name a few) in this paediatric population should be provided.

2- A **thorough safety review of all patients with iron chelators combinations containing Exjade** in this observational study should be provided to describe the safety profile of such combinations in real life, especially in those paediatric patients (beta-thalassemic and SCD). Also the MAH should try to analyse the reasons why prescribers used such combinations (in therapeutic strategy).

3- The MAH should clarify in the fatal GI haemorrhage case occurring in a 16 years-old female patient how the MAH has the information that "GI haemorrhage is not related to Exjade as it occurred in a context of oesophageal variceal" while in CIOMs form of the case in EV, no such information is recorded.

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

MAH responses to Request for supplementary information

Question 1:

Too many discrepancies have been identified to correctly assess the safety data recorded in this study CICL670ATR03. Therefore, the MAH is requested to provide a correct comprehensive safety analysis of this study (for SAE and non SAE occurring during therapy including Exjade) with analysis of time to onset, circumstances of occurrence, potential risk factors, predisposal factor, dechallenge/rechallenge, outcome, action taken with the product…). Also, an additional review of events of interest (such as renal,

hepatic disorders, hearing abnormalities, long term events (related to time exposure) … to name a few) in this paediatric population should be provided.

MAH's response

A statistical analysis plan addendum for study CICL670ATR03 has been developed. The complementary data provide additional evidence for deferasirox safety in the CICL670ATR03 study population <18 years of age (N= 458).

Adverse events and serious adverse events, regardless of study drug relationship, by primary system organ class, preferred term and treatment are presented in [Tables 1 and 2 of Appendix 3].

The population for the new/revised analysis only includes patients <18 years of age treated with Exjade only (N=457) and treated with Exjade combined with other another iron chelator (Desferal) (N=1).

In this observational study the majority of the observed 483 pediatric patients with transfusional iron overload were diagnosed with beta-thalassemia (n=459). Twenty four patients were diagnosed with sickle cell disease (n=24).

The observed safety profile of iron chelation including deferasirox in this paediatric patient population diagnosed with beta thalassemia or sickle cell disease is in line with the known safety profile of deferasirox in single agent use and with the known complications and procedures of the underying diseases. No new signals have been observed in general, including for sytem organ classes of special interest inclusing renal, hepatic, ophthalmic and acustic or skin related adverse events.

While treatment discontinuations for other reasons have been observed in the study population, discontinuations due to adverse events were rare [Table 3 of Appendix 3]. Four patients were observed to have discontinued iron chelation due to the adverse event bone marrow transplantation for the underlying condition beta thalassemia. Bone marrow transplantation is a common treatment option for pediatric patients diagnosed with beta thalassemia. The majority of patients who were treated with deferasirox and underwent bone marrow transplantation (n=23) completed the study prior to transplant. Two patients discontinued due to renal tubular disorders and information is provided below in association with [Table 3 of Appendix 3].

In the study population treated with deferasirox, renal adverse events were observed. One patient who experienced the event of nephrolithiasis also experienced urinary tract infection. Three events of proteinuria and 1 investigation of protein urine presence were described in this study the latter was reported to be related to study drug by the investigator. Deferasirox treatment was continued or patients were managed with dose reduction in the sole event of proteinuria. Proteinuria is a commonly described adverse event for patients treated with deferasirox [Tables 4, 5 and 6 of Appendix 3].

One SAE and two AE of renal tubular disorders were reported. The patient with the SAE of renal tubular disorder was reported as renal tubulopathy related to deferasirox by the investigator. This 11 year old female with beta thalassemia major, experienced kidney tubule disorder and abdominal pain. She was receiving 625 mg (26 mg/kg/day) of Exjade daily. The study drug was permanently discontinued due to the event renal tubulopathy, and both events resolved. Renal tubulopathy has been reported in patients treated with deferasirox. The majority of these patients were children and adolescents with beta-thalassemia and serum ferritin levels <1,500 microgram/L.

There was no new safety signal for renal and urinary disorders in the pediatric population treated with deferasirox within the 3 year observation period.

Additional analysis for the event of increased liver enzymes indicate that patients may experience liver enzyme elevation throughout the observational period. The Kaplan-Meier estimate supports the association of risk to experience an increase of liver enzymes with increasing duration of drug exposure [Figure 1 of Appendix 3]. However for the documented 9 cases treated with deferasirox the increase was mild (Grade 1-2) and transient in nature for most of the patients [Figure 2 of Appendix 3]. Most patients with hepatic enzyme increase we managed with dose interruption. No patient discontinued from study solely due to the event increased liver enzymes.

Overall, there were no unexpected safety findings based on the additional assessments performed in this pediatric patient population under long-term deferasirox treatment. Importantly, no clinically significant changes in liver or kidney function were observed in the study period. The safety profile for pediatric patients of study CICL670ATR03 remains consistent with the known profile of deferasirox.

Assessment of the MAH's response

As a general comment, the safety assessment in paediatric population was not the primary objective of this study ATR03. Only descriptive data were recorded.

We consider that the MAH's response is not acceptable. Firstly, the MAH has not clarified all the discrepancies identified by the CHMP in the preliminary assessment report. Secondly, the MAH has not provided a comprehensive safety review updated with all key elements requested by the CHMP. Indeed, the MAH has not provided serious adverse events with suspected relationship to study drug. Additionally, AEs with suspected relationship to study drug were given succinctly (i.e. without circumstances of occurrence, outcome…). AEs causing study drug discontinuation, requiring dose adjustment and study drug interruption are given regardless of study drug. Also the MAH provided only a succinct review of events related to renal and hepatic events.

Therefore, the CHMP cannot draw any conclusion on the safety profile of Exjade in paediatric population based on this study analysis, as the data are too scarce.

We can agree that this study is not designed specifically to assess the safety (due to the descriptive nature of data). Nevertheless, uncertainties on safety in youngest patients treated with Exjade remain due to this incomplete analysis of registry's results.

Therefore, we consider with great importance the MAH's response to the safety questions raised in the variation II48 regarding the long term safety in paediatric patient aged from 2 to 6 years-old (still ongoing) as the same questions regarding renal and hepatic disorders and long term events are requested to be clarify.

We strongly recommend to MAH to provide a comprehensive safety analysis of A2411 study results (with specific analysis of renal/hepatic parameters to name a few) in the context of variation II48.

Issue partially addressed.

Question 2:

A thorough safety review of all patients with iron chelators combinations containing Exjade in this observational study should be provided to describe the safety profile of such combinations in real life, especially in those paediatric patients (beta-thalassemic and SCD). Also the MAH should try to analyse the reasons why prescribers used such combinations (in therapeutic strategy).

MAH's response

For clarification regarding the cases of combination therapy, a detailed medical review was performed. It was confirmed that "combination therapy" was regarded as any supportive therapy

administered at any point during the observation period and not specifically as the concomitant use of deferasirox with other iron chelators.

Table 3-1 provides an overview of patients who were confirmed to be treated with an iron chelation combination during the study. Only one of the initially reported 55 paediatric patients receiving more than one iron chelator, actually received deferasirox *concomitantly* with another iron chelator (Desferal). The narrative of this single case of iron chelation combination therapy with deferasirox is provided below.

A total of 12 patients received a combination of iron chelators (i.e. Desferal and Ferriprox) not concomitantly with deferasirox therapy (either without deferasirox or with deferasirox in a sequential manner).

- Two of the 12 patients received the combination of Desferal (deferoxamine) and Ferriprox (deferiprone) simultaneously and no other iron chelation during the study.
- Ten of these 12 patients received the same combination of deferoxamine plus deferiprone sequentially too but sequentially to other iron chelators throughout the observation period.
- Nine patients received Exjade sequentially to another iron chelator.

Table 3-1 Paediatric patients confirmed to be treated with an iron chelation combination

	Center No	Diagnosis	Iron chelator	Start date	Stop date	Reason to stop treatment	Treatment Duration	ICT received during observation
1	01_15	Beta-thalassemia	Exjade	24.11.2009	26.01.2012	Change in treatment due to the high ferritin	26	Exjade, Ferriprox, Desferal+Ferriprox
			Ferriprox	26.01.2012				
			Desferal	23.05.2013				
2	08_06	Beta-thalassemia	Exjade	19.11.2008	25.11.2010	Weight gain	25	Exjade, Desferal+Ferriprox
			Exjade	25.11.2010	23.02.2011	Increase in ferritin value	3	
			Exjade	23.02.2011	18.08.2011	Exjade stopped, Therapy changed	6	
			Desferal	18.08.2011				
			Ferriprox	18.08.2011				
3	08_28	Beta-thalassemia	Exjade	02.12.2008	23.08.2012	Increase in ferritin value	45	Exjade, Desferal+Ferriprox
			Exjade	23.08.2012	12.03.2013	Increase in ferritin value	7	
			Exjade	12.03.2013	11.04.2013	Exjade stopped, AST, ALT increased	1	
			Desferal	11.04.2013				
			Ferriprox	11.04.2013				
4	08_30	Beta-thalassemia	Desferal	05.02.2010	23.10.2012		33	Desferal+Ferriprox
			Ferriprox	05.02.2010	23.10.2012	Ferritin increased	33	
			Ferriprox	23.10.2012				
5	19_45	Beta-thalassemia	Desferal	01.01.2008	02.02.2011	High ferritin levels	38	Exjade, Desferal+Ferriprox
			Ferriprox	01.01.2008	02.02.2011	Treatment change	38	
			Exjade	02.02.2011	27.01.2013	High ferritin levels	24	
			Exjade	27.01.2013	19.12.2013	Low ferritin levels	11	

	Center No	Diagnosis	Iron chelator	Start date	Stop date	Reason to stop treatment	Treatment Duration	ICT received during observation
			Exjade	19.12.2013				
		Beta-thalassemia	Desferal	09.09.2005	08.03.2010	treatment non-compliance	55	Desferal, Exjade, Desferal+Ferriprox
			Ferriprox	25.03.2009	08.03.2010	Arthralgia	12	
			Exjade	08.03.2010	19.10.2011	Increase in ferritin value	20	
			Exjade	19.10.2011	23.07.2012	Increase in ferritin value	9	
6	21_01							
			Exjade	23.07.2012	03.12.2012	Tubulopathy, Exjade suspected.	4	
			Exjade	03.12.2012	25.02.2013	Tolule	3	
			Exjade	25.02.2013	15.05.2013	Weight gain	3	
			Exjade	15.05.2013				
		Beta-thalassemia	Desferal	24.05.2004	22.10.2008	treatment non-compliance	54	Desferal, Desferal+Ferriprox, Exjade
			Ferriprox	31.03.2008	07.08.2008	Neutropenia developed	4	
			Exjade	22.10.2008	04.02.2010		16	
7	21_05		Exjade	04.02.2010	06.05.2010	Ferritin reduced	3	
			Exjade	06.05.2010	31.01.2011	Increase in ferritin value	9	
			Exjade	31.01.2011	25.07.2012	Ferritin reduced	18	
			Exjade	25.07.2012	26.06.2013		11	
			Exjade	26.06.2013		Weight gain		
		Beta-thalassemia	Desferal	29.12.1999	14.09.2009	treatment non-compliance	118	Desferal, Desferal+Ferriprox, Exjade
			Ferriprox	04.04.2008	14.09.2009	treatment non-compliance	18	
8	21_08		Exjade	14.09.2009	15.07.2010	Ferritin reduced	10	
			Exjade	15.07.2010	18.04.2011	Weight Gain	9	
			Exjade	18.04.2011	22.12.2011	Increase in ferritin value	8	
			Exjade	22.12.2011	01.08.2012	Ferritin reduced	7	

	Center No	Diagnosis	Iron chelator	Start date	Stop date	Reason to stop treatment	Treatment Duration	ICT received during observation
			Exjade	01.08.2012	11.12.2012	Weight gain	4	
			Exjade	11.12.2012	09.01.2013	Ferritin reduced	1	
			Exjade	09.01.2013				
		Beta-thalassemia	Desferal	01.01.2008	16.06.2010	High ferritin level	30	Desferal, Desferal+Ferriprox, Exjade
9	25_19		Ferriprox	05.11.2009	16.06.2010	High ferritin level	7	
			Exjade	16.06.2010	07.09.2011	High ferritin level	15	
			Exjade	07.09.2011				
		Beta-thalassemia	Desferal	28.04.2011				Desferal+Ferriprox
10	29_25		Ferriprox	28.04.2011				
		Sickle cell anemia	Exjade	26.05.2009	16.07.2012	Increase in ferritin value	38	Exjade, Exjade+Desferal
			Exjade	16.07.2012	26.11.2012	Increase in ferritin value	4	
11	44_02		Exjade	26.11.2012	17.12.2012	High level of ferritin	1	
			Desferal	26.11.2012	14.06.2013		7	
			Exjade	17.12.2012				
			Desferal	10.07.2013				
		Beta-thalassemia	Desferal	21.07.2011	23.01.2012		6	Desferal+Ferriprox,Ferriprox
12	45_05		Ferriprox	21.07.2011	23.01.2012		6	
			Ferriprox	23.01.2012				
		Beta-thalassemia	Ferriprox	15.11.2011	16.12.2011		1	Ferriprox, Desferal+Ferriprox, Exjade,Desferal
13	45_30		Ferriprox	16.12.2011	13.07.2012		7	
			Ferriprox	13.07.2012	07.11.2012		4	
			Ferriprox	07.11.2012	08.02.2013		3	
			Desferal	04.01.2013	08.02.2013		1	

Center No	Diagnosis	Iron chelator	Start date	Stop date	Reason to stop treatment	Treatment Duration	ICT received during observation
		Exjade	08.02.2013	15.03.2013		1	
		Desferal	24.05.2013	04.12.2013		6	
		Desferal	04.12.2013				

Report

The initial report was received from an investigator on 11-Apr-2013 regarding a 24-year-old Caucasian male with aplastic anemia, who experienced infection due to gastroenteritis on 26-Nov-2012 and was hospitalized. On 04-Dec-2012, the patient was recovered. On 17-Jan-2013, the patient experienced gastroenteritis and was again hospitalized. On the same day, stool examination was performed but no pathogen was identified.

The patient recovered on 23-Jan-2013. On an unspecified date the patient experienced abdominal pain with mild intensity daily. Platelet and neutrophil counts were below normal limits, consistent with the underlying aplastic anemia. Iron chelation treatment was continued. The outcome of the events “infection due to gastroenteritis” and “gastroenteritis” was reported as complete recovery and for abdominal pain it was not reported. These events gastroenteritis, infection were not assessed for seriousness by the investigator, but were conservatively upgraded to SAEs by Novartis on processing. The causality of all the events was reported as not suspected by the investigator.

In conclusion the SAE of gastroenteritis was treated adequately and the event resolved. Iron chelation treatment was maintained.

Assessment of the MAH’s response

The review requested on the combination of iron chelators was performed by the MAH:
a total of 13 patients received a combination of iron chelators. Twelve of them received Desferal® and Ferriprox® and one of them received Exjade® and Desferal®. The single patient who received iron chelator combination containing Exjade® experienced gastroenteritis, infection due to gastroenteritis and abdominal pain. The outcome of the events “infection due to gastroenteritis” and “gastroenteritis” was reported as complete recovery and for abdominal pain it was not reported. The causality of all these events was reported as not suspected by the investigator. Besides iron chelation treatment was maintained.
As requested, the MAH has provided reasons why prescribers used iron chelators combinations. It was generally due to a high level of ferritin or an increase of ferritin value. For the patient and patient, the MAH did not give the reasons of the use of iron chelators combination.

Issue addressed

Question 3:

The MAH should clarify in the fatal GI haemorrhage case occurring in a 16 years-old female patient how the MAH has the information that “GI haemorrhage is not related to Exjade as it occurred in a context of oesophageal variceal” while in CIOMs form of the case in EV, no such information is recorded.

MAH’s response

This report refers to a 16-year-old female patient with a medical history of beta-thalassemia major. Concomitant medications included folic acid and zinc. The patient started treatment with Exjade in 2006 at a dose of 30 mg/kg/day for the treatment of iron overload. Platelet count at baseline (unknown date) was normal with 191,000 cell per mm3. On 25-Apr-2013 (2,491 days after start treatment with Exjade), the patient had upper gastrointestinal system bleeding; treatment with Exjade was stopped. At the time of bleed, the platelet count was elevated with 704,000 cells per

mm3. On 26-Apr-2013, the patient died due to gastrointestinal hemorrhage. The causality of the event was reported as not related to Exjade by the investigator.

The apparent discrepancy found by EMA in the medical history in regards to esophageal varices is due to the fact that the clinical database had been subsequently updated with this historical condition and the pharmacovigilance database, from which the CIOMS was generated, was not.

The company assessed this case as unlikely to be related to Exjade. The event of gastrointestinal haemorrhage in this subject has a time to drug intake that makes relationship improbable and other disease, presence of esophageal varices, provide plausible explanations according to WHO-Uppsala Monitoring Center Causality Assessment System.

Assessment of the MAH's response

Clarifications have been given. Issue addressed.

MAH's conclusion

Overall, there were no unexpected safety findings based on the additional assessments performed in this paediatric patient population under long-term deferasirox treatment analyses for CICL670AUS38 and CICL670ATR03.

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

No changes to the paediatric information of the current Exjade (deferasirox) Core Data Sheet are proposed as a result of these additional data, and no regulatory consequences of the submitted study are anticipated for the pediatric information in the EU Summary of Product Characteristics.

5. CHMP overall updated conclusion and recommendation

Efficacy

As a general comment, efficacy conclusions are difficult to drawn since efficacy of deferasirox is not a primary objective of this observational study. Only descriptive data are available.

In the study ATR03, reduction in mean SF, improvement of cardiac (T2* > 20 ms) parameters relative to cardiac iron overload was observed for DFX treated patients with b-TM or SCD at 3 years. However, the study design cannot allow to conclude on efficacy of DFX on cardiac and liver iron overload.

Safety

In the study ATR03 (transfusion dependant hemoglobinopathies : beta thalassemic/SCD population): No unexpected event was observed. Delayed sexual development was reported in both genders within 2 age-groups: 7-12 years-old and 13-18 years-old. Even if we take into account limitation of data collected (Tanner staging not performed), we consider that these finding should be kept in mind as they are not consistent with the previous analyses of study 107E1 (follow-up of 5 years of beta-thalassemic patients).

Also, too many discrepancies have been identified to correctly assess the safety data recorded in this study. Therefore, the CHMP cannot draw any conclusion on the safety profile of Exjade in paediatric population based on this study analysis, as the data provided by the MAH is too scarce.

We can agree that this study is not designed specifically to assess the safety (due to the descriptive nature of data). Nevertheless, uncertainties on safety in youngest patients treated with Exjade remain due to this incomplete analysis of registry's results.

Therefore, we consider with great importance the MAH's response to the safety questions raised in the variation II48 regarding the long term safety in paediatric patient aged from 2 to 6 years-old (still ongoing) as the same questions regarding renal and hepatic disorders and long term events are requested to be clarify.

We strongly recommend the MAH to provide a comprehensive safety analysis of A2411 study results (with specific analysis of renal/hepatic parameters to name a few) in the context of variation II48.

☒ Fulfilled:

No regulatory action required.