28 April 2016
EMA/331072/2016
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/P46/066

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

Table of contents

1. Introduction

On 30 September 2015, the MAH submitted one completed paediatric study 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 this study is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

This was a phase IV, non-interventional, observational study. Patients were treated with an oral iron chelator according to the investigator's judgment and in accordance with the local prescribing information. 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 the final report for:

- CICL670AUS38 : A 3 year, prospective, non-interventional multicentre registry in sickle cell disease patient

2.3.2. Clinical study

CICL670AUS38 : A 3 year, prospective, non-interventional multicentre registry in sickle cell disease patient

Description

This is a 3 year, prospective, multicentre, observational study (registry) which included adults and children (2-<18 years at enrolment) with SCD. The study was conducted in US to enhance the understanding of the disease patterns, current transfusion practices, treatment and document clinical outcomes in patients with SCD under current treatment practices.

Methods

Objective(s)

Primary objective

☐ The primary objective for the study was to document clinical outcomes (number of crises, number of hospitalizations, and end organ damage) in patients with sickle cell disease (SCD) under current treatment practices.

Secondary objectives

The secondary objectives included the following:

☐ To document the current therapies used, transfusion practices, and use of chelation therapies for the treatment of SCD

☐ To evaluate the difference in treatments between pediatric and adult patients

☐ To assess the Quality of Life (QoL) by PedsQLTM Pediatric Quality of Life Inventory for patients aged 2 to < 18 years, and by SF-36® Health Survey for patients aged ≥ 18 years

☐ To evaluate the impact of disease in school and work absentee rates

☐ To evaluate the correlation between

- o Pre-transfusion hemoglobin and patient outcomes;
- o Transfusion practices and patient outcome;
- o Chelation practices and patient outcome.

Study design

The recruitment target was 500 patients with HbSS, HbS/beta-thalassemia or HbSC and divided into 2 cohorts :

Cohort 1 (paediatric) : aged 2- <18 years-old

Cohort 2 (adults) : aged >18 years-old

The patients were followed for a maximum of 3 years. The study was initiated on January 13,2010 (FPFV) and ended on September 30,2014 (LPLV). The study was conducted in 54 sites in US.

CHMP comment

This is an observational study which is not designed to assess the efficacy of chelation therapy (in particular deferasirox).

Study population /Sample size

A total of 500 patients were planned to enroll into 2 cohorts.

A total of 498 patients (**317 patients aged 2 to less than 18 years** and 181 patients aged 18 years and older) were enrolled in this study, all were analyzed.

Inclusion criteria

☐ Male or female patients with HbSS, HbS/beta-thalassemia, or HbSC

☐ Patients must be aged ≥ 2 years

☐ Patients or legal guardians must provide a written informed consent, and pediatric assent where indicated

Exclusion criteria

☐ Patients with Sickle Cell trait (HbAS)

☐ Patient or legal guardians unable or unwilling to give consent or pediatric assent where indicated

Treatments

There were no particular treatment or drug given to patients and there were no predefined treatment groups. No clinical or laboratory assessments were performed other than those required for disease management according to local best practice.

Outcomes/endpoints

Statistical Methods

Sample size

The sample size of this study was not based on any statistical considerations. It was based on the feasibility to achieve a broad representation of SCD patients within a reasonable enrollment period.

Data analysis

The data were analyzed by Novartis and/or the designated CRO and summarized with respect to demographic and baseline characteristics, concomitant medications, primary and secondary endpoints, and safety observations. Data were summarized descriptively and presented by follow-up visits (every 6 months).

Analysis sets

The Full Analysis Set (FAS) was the primary set for all analyses, which included all patients who enrolled in the registry.

Analysis of primary endpoints

The data collected for primary endpoints included frequency of crises and end organ damage (as specified above), frequency of hospitalizations, and overall survival. The data were analyzed descriptively (counts and percentages) and presented overall and by age cohort.

The associations between transfusions, chelation, ferritin, and clinical outcomes were also explored.

Results

Recruitment/ Number analysed

A total of 498 patients were enrolled in the study **(317 pediatric patients** and 181 adult patients).

Baseline data

A total of 124 patients (24.9%) had exposure to chelation therapies at baseline. A higher percentage of adult patients received prior chelation therapies compared with paediatric patients (33.7% vs 19.9%). The most commonly used prior chelation therapies were deferasirox and deferoxamine

A total of 152 patients (30.5%) received chelation therapy sometime during their lifetime, with a significantly higher percentage of adult patients compared with paediatric patients (*P* = 0.0014). The cumulative median exposure to chelation therapies used was higher in adult patients 71 (39.2%) compared with paediatric patients 81 (25.6%). The most commonly used chelation therapies were deferasirox and deferoxamine. During the study, **64 (20.2%) of 317 paediatric patients** and 51 (28.2%) of 181 adult patients **received deferasirox** while deferoxamine was used in 7 (2.2 %) of paediatric and 6 (3.3%) of adult patients. One (0.6%) adult patient was treated with deferiprone.

CHMP comment

Among patients receiving iron chelators, 96.8% (61/63) paediatric patients were already on deferasirox therapy. Also, 30% (19/63) pediatric patients were already on deferoxamine. As the median duration of chelation therapy is around 4 years (1546.5 days), we can extrapolate that the paediatric patients enrolled in this registry well tolerated Exjade already.

Efficacy results

The mean serum ferritin (SF) concentration at baseline was 2355.77 µg/L in pediatric patients (n = 59) and 3527.72 µg/L in adult patients (baseline, n = 33) and at the study end, the mean SF levels were 2584.38 µg/L (n=44) and 3913.46 µg/L (n=28), respectively .

CHMP comment

This is an observational study which is not designed to assess the efficacy of chelation therapy (in particular deferasirox).

Although this study was not designed to assess efficacy (no efficacy in primary and secondary objectives) the apparent increase in serum ferritin between baseline and end of the study should be more discussed (mean serum ferritin (SF) concentration from 2355.77 µg/L at baseline (n=44) and 2584.38 µg/L (n = 59) at the end of the study in pediatric patients).

Safety results

4.2 DFX treated patients

4.2.1 Adverse events:

Overall, the incidence of adverse events in patients treated with DFX was comparable between paediatric and adult patients (38; 59.4% and 32; 62.7%), respectively. The most commonly affected primary SOC class in both groups was General disorders and administration site conditions 15 (23.4%) and 28 (54.9%).

Among the pediatric population, the most frequently AEs reported by ≥5% of patients by preferred term were pain 7 (10.7%), abdominal pain, headache, pyrexia , pain in extremity (6; 9.4% each), acute chest syndrome 5 (7.8%) and back pain 4 (6.3%), Similarly, the most commonly reported AEs for adults were pain 22 (43.1%), pyrexia 9 (17.6%), pneumonia 7 (13.7%), anaemia 6 (11.8%), skin ulcer, diarrhoea (5; 9.8% each), abdominal pain, wheezing, nausea , sickle cell anaemia with crisis, urinary tract infection, bronchitis (4; 7.8% each), fatigue, abdominal pain upper, back pain , headache, oropharyngeal pain , pulmonary hypertension (3; 5.9% each).

The incidence of adverse events suspected to be related to deferasirox was numerically lower in paediatric patients vs adult patients (3; 4.7%) and (7; 13.7%), respectively. The suspected adverse events in paediatric patients were **aspartate aminotransferase increased, blood bilirubin increased, abdominal pain , abdominal pain upper , hypoaesthesia , paraesthesia , rash (1; 1.6% each).** In adult patients, those were diarrhoea 3 (5.9%), sickle cell anaemia with crisis and pain (2; 3.9% each), nausea , abdominal pain upper , acute renal failure (1; 2% each).

The adult patient who experienced acute renal failure had a complete recovery from the event after the study drug interruption. Ii is unknown if deferasirox was reintroduced after the recovery. Of note, the investigator stated that the cause of the patient's renal insufficiency (injury) was multifactorial, hemosiderosis being a contributing factor. Furthermore, the patient was also receiving levofloxacin for UTI and investigator reported that the event acute kidney injury could be possibly related to the treatment medication.

CHMP comment

A total of 7 AEs (all non serious and mild/moderate) were considered suspected to be related to Exjade in paediatric population (instead of 3 mentioned by the MAH). The suspected adverse events in paediatric patients were AST increased, blood bilirubin increased, abdominal pain, abdominal pain upper, hypoaesthesia , paraesthesia , rash (1; 1.6% each).

The overall safety profile was consistent with the known safety profile of Exjade and complications of underlying condition

4.2.2 Serious Adverse Events

The incidence of serious adverse events (SAEs) in DFX patients, regardless of causality, at the study end was numerically slightly lower in paediatrics compared with adults 29 (45.3%) and 29 (56.9 %), respectively. The majority of SAEs were classified as severe: paediatric 23 (35.9%) and adults 26 (51%). In the paediatric patients, the most commonly SAEs were reported in the following System Organ Class (SOC): General disorders and administration site conditions 12 (18.8%), Musculoskeletal and connective tissue disorders 8 (12.5%), Gastrointestinal disorders 7 (10.9%). Most common SAEs, reported by ≥ 5% of patients by preferred term, were **pain (7; 10.9%), pyrexia, pain in extremity**

and acute chest syndrome (ACS) (5; 7.8% each), abdominal pain and back pain (4; 6.3% each).

In the adult patients, the following most commonly SOCs were reported: General disorders and administration site conditions 25 (49.0%), Infections and infestations 10 (19.6%) Musculoskeletal and connective tissue disorders 4 (7.8%). Most common SAEs, reported by ≥ 5% of patients by preferred term, were pain (21; 41.2%), pneumonia (7; 13.7%), anaemia (5; 9.8%), sickle cell anaemia with crisis, abdominal pain, pyrexia and skin ulcer (4; 7.8% each), back pain (3; 5.9%).

CHMP comment

Most common SAEs, reported by ≥ 5% of paediatric patients were pain (7; 10.9%), pyrexia, pain in extremity and acute chest syndrome (ACS) (5; 7.8% each), abdominal pain and back pain (4; 6.3% each). These SAEs were considered as not related by the MAH: SCD complications included events such as pain, acute chest syndrome; SCD crisis.

The overall safety profile was consistent with the known safety profile of Exjade and complications of underlying condition

4.2.3 Death:

Among the 2 patients who received DFX during the study, one SCD pediatric patient (0046-00006), 17 year-old male, experienced **severe multi-organ failure** leading to hospitalization and subsequently died due to **Acute Chest Syndrome** (ACS). The patient was treated with poly medications for sickle cell anaemia complications and was receiving deferasirox prior to experiencing death. The Investigator did not suspect a relationship between the multiple organ failure and the study medication.

The other SCD patient, 33 year-old male, presented with severe gastrointestinal hemorrhage and concomitant disease progression leading to hospitalization. The patient died due to liver failure secondary to hepatitis C. During the event, the patient was treated with multiple medications and was receiving DFX. The Investigator did not suspect a relationship between the events gastrointestinal hemorrhage, concomitant disease progression, and hepatic failure and the study medication.

CHMP comment

In the paediatric population, one fatal case was reported in a patient treated with deferasirox. The causal relationship between Exjade and the occurrence of fatal acute chest syndrome is doubtful considering his medical history (SCD complications: lung disorders, respiratory distress and wheezing) and his polymedication for SCD complications.

4.2.4 Renal and hepatic assessments

The mean SGPT (ALT) at the baseline was 29.6 U/L for paediatric patients (n=63) and 38.3 U/L for adult patients (n=46) and they remained within normal range consistently throughout the study. At the study end the mean ALT was 31.9 (n=49) and 42.7 U/L (n=35), respectively.

The mean baseline SGOT (AST) was slightly elevated in both cohorts: 52.7 U/L in pediatric (n=63) and 55.8 U/L in adults (n=46). These levels remained consistent within the study and EOS mean was 52.7 U/L (n=49) and 57.5 U/L (n=35), respectively.

The mean serum creatinine (SCr) concentration at baseline was numerically higher in adult patients (62.2 µmol/L, n = 47) versus pediatric patients (34.5 µmol/L, n = 64); both within normal range. In pediatric patients, the mean SCr remained consistent at all study visits but visit 4 (84.3 µmol/L, n=51). At the study end, the mean SCr in paediatric patients returned to near baseline level and was 38.8 µmol/L (n=48). Adult patients showed slight increase in mean SCr concentrations from baseline to the end of study (70.7 µmol/L, n = 35).

CHMP comment

These data are mainly average of full set analysis. However, based on the data provided, it cannot be assessed if there is an impact of duration of therapy with Exjade in real life to hepatic/renal parameters in a specific category of patients. Therefore, the MAH should provide a table with the frequency of relative change from baseline to EOS for each hepatic (AST, ALT) and renal parameters (ClCr if available) by treatment duration in the paediatric population.

4.2.5 Pain Crisis

In a comparison to the 11 (21.6%) DFX adult patients, a higher proportion of paediatric DFX patients (35; 54.7%) did not experience pain crisis in the 5 years prior to the baseline visit. During the study, the proportion of DFX paediatric patients experiencing pain crisis (44; 68.8%) was numerically less when compared to adults (45; 88.2%). The mean number of pain crises was 4.5 (SD, 4.67) for children and 7.2 (SD, 8.20) for adults. In terms of severity of pain crises, majority were severe and required hospitalization. The majority of the pain crisis episodes in paediatric patients persisted for 1 to 3 days as opposed to adults <1 day.

CHMP comment

Pain crisis is one of the known SCD complications. During the study, the proportion of DFX paediatric patients experiencing pain crisis (44; 68.8%) was numerically less when compared to adults (45; 88.2%). But the majority are still severe.

4.2.6 Acute Chest Syndrome

In the 5 years prior to the baseline visit, 70.3% of paediatric patients and 88.2% of adult patients receiving DFX were free from ACS. Within the study, a higher occurrence of ACS was observed in paediatric patients as opposed to adults: 28 (43.8%) and 12 (23.5%) respectively. The mean number of ACS episodes was 2.6 (SD, 1.84) for children and 1.6 (SD, 1.16) for adults. The majority of ACS episodes persisted for <10 days.

CHMP comment

Acute Chest syndrome is one of the known SCD complications.

Within the study, a higher occurrence of ACS was observed in paediatric patients treated with Exjade as opposed to adults: 28 (43.8%) and 12 (23.5%) respectively. This tendency was already observed at baseline. Similarly for the overall paediatric population of the study, this tendency was also observed.

However, no significant difference was noted between ACS incidence in overall paediatric population (135 / 317; 42.6%) and in paediatric population treated with Exjade within the study (23/64; 43.8%).

4.2.7 Infection

In the 5 years preceding the baseline visit, comparable proportions of deferasirox paediatric 70.3% and adult 64.7% patients had no infections. No difference for incidence of infections was observed between paediatric and adult patients treated with deferasirox during the study: 42.2% (27 patients) and 47.1% (24 patients) respectively. The mean number of infections was 2.3 (SD, 1.39) for children and 2.7 (SD, 3.16) for adults. The majority of infections continued for <10 days.

CHMP comment

Infection is one of the known SCD complications. No difference for incidence of infections was observed between paediatric and adult patients treated with deferasirox during the study

4.2.8 Stroke

Prior to the 5 years preceding the baseline visit, 81.3% of paediatric and 76.5% of adult patients treated with deferasirox did not experience stroke. Of those who experienced stroke there were 6 paediatrics and 12 adults and most of the events occurred in the first year. Of note, data on 6 paediatric patients was missing. Within the study, there were 15 (23.4%) paediatric and 3 (5.9%) adult patients who presented with stroke while receiving DFX. Among these few patients, the mean number of strokes was 1.2 (SD, 0.56) for children and 1.0 (SD, 0.00) for adults.

CHMP comment

Stroke is one of the known SCD complications.

At baseline, in Exjade treated patients, there were 6 (9.4%) children and 12 (21.6%) adults who had presented with stroke prior to last 5 years. Within the study, there were **15 (23.4%) paediatric** and 3 (5.9%) adult patients who presented with stroke while receiving DFX.

Also, in the full set analysis (overall population), at baseline, there were 9 (2.8%) children and 17 (9.4%) adults who had presented with stroke prior to last 5 years. Within the study, there were **16 (5%) paediatric** and 7 (3.9%) adult patients who presented with stroke while receiving DFX.

Therefore, the majority of stroke in paediatric patients in this observational study seems to appear in paediatric patients treated with Exjade (15 of the 16 cases). Even if this is based on few patients, this issue is important to consider. The MAH should review all paediatric cases of stroke under Exjade therapy.

4.2.9 Priapism

Prior to the 5 years preceding the baseline visit, 94.3% paediatric and 72.7% adult patients treated with deferasirox were free of priapism. Of those who experienced priapism prior to the baseline visit, there was one (2.9%) pediatric and 5 (22.6%) adult patients. Data for one patient in each group was missing. During the study, there were no patients with priapism in <18 years of age group and there were 6 (27.3%) adult patients who had episodes of priapism.

CHMP comment

Priapism is one of the known SCD complications. During the study, there were no patients with priapism in <18 years of age group and there were 6 (27.3%) adult patients who had episodes of priapism.

MAH's conclusions

Iron overload (IOL) is an inevitable consequence of frequent blood transfusion which in turn is associated with debilitating clinical complications.

The limitation of this study is related to its design as single arm observational which did not mandate any specific treatment and/or diagnostic procedures.

During the study, a slight increase in serum ferritin levels was observed in both patient groups.

This suggests that patients were inadequately controlled for iron overload. Since serum ferritin is an acute-phase reactant, interpretation in SCD is confounded by the presence of a strong inflammatory component in these patients.

Furthermore, the study was not designed to assess efficacy of chelation therapy and the compliance was not monitored either. Thus, one cannot conclude on the effect of DFX on iron removal in the observed population.

Overall, there were no unexpected safety findings observed regarding AEs or SAEs in both pediatric and adults patients. No death was suspected to be related to DFX as assessed by the investigator. An adult patient who died due to liver failure experienced gastrointestinal bleeding both events not suspected to be related to the study drug. Of note, gastrointestinal haemorrhage and hepatic failure have been reported in patients receiving EXJADE. These events were added to the SPC and are present in the approved labeling.

Within the study, there was no clinically significant change in liver or kidney function in patients receiving DFX. There was one adult patient who presented with acute renal failure which was suspected to be related to DFX. After the drug interruption, the patient had a complete recovery for the event. Of note, cases of acute renal failure have been reported following post-marketing use of DFX and the SPC was subsequently updated with the relevant information.

Some differences between incidences of complications in pediatric and adult patients were seen within the study, reflecting the course of the disease and its clinical presentation. For instance, more paediatric patients experienced stroke. This is not unexpected as the highest incidence of first infarction is seen in children with the incidence decreasing between the ages of 20 and 29 years.

CHMP comment

As a general comment, this is an observational registry which is not designed to assess the efficacy of chelation therapy (in particular deferasirox). However, an apparent increase in serum ferritin between baseline and end of the study was observed (mean serum ferritin (SF) concentration from 2355.77 µg/L at baseline (n=44) and 2584.38 µg/L (n = 59) at the end of the study in pediatric patients). The MAH suggests that patients were inadequately controlled for iron overload. The MAH should more discuss the value of maintaining deferasirox in this population.

The safety assessment of Exjade in paediatric population was not the primary objective of this study AUS38. Only descriptive data were recorded.

One fatal case was reported in a young patient treated with deferasirox (multiorgan failure and acute chest syndrome) but the relationship with Exjade is doubtful (patient polymedicated due to SCD complications prevention and medical history of lung disorders).

The suspected adverse events in paediatric patients were aspartate aminotransferase increased, blood bilirubin increased, abdominal pain , abdominal pain upper , hypoaesthesia , paraesthesia , rash (1; 1.6% each).

Pain crisis, acute chest syndrome, infections, stoke and priaspism are known SCD complications.

The overall safety profile was consistent with the known safety profile of Exjade and complications of underlying condition. However, based on the data provided, it cannot be assessed if there is an impact of duration of therapy with Exjade in real life to hepatic/renal parameters in a specific category of patients. Therefore, the MAH should provide a table with the frequency of relative change from baseline to EOS for each hepatic (AST, ALT) and renal parameters (ClCr if available) by treatment duration in the paediatric population.

Stroke is one of the known SCD complications. The majority of stroke in paediatric patients in this observational study seems to appear in paediatric patients treated with Exjade (15 of the 16 cases). Even if this is based on few patients, this issue is important to consider. The MAH should review all paediatric cases of stroke under Exjade therapy.

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 AUS38, an apparent increase in serum ferritin between baseline and end of the study was observed in pediatric patients with SCD. The MAH suggests that patients were inadequately controlled for iron overload. The MAH should more discuss the value of maintaining deferasirox in this population.

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 AUS38, 64 (20.2%) of 317 paediatric patients and 51 (28.2%) of 181 adult patients received deferasirox. As the median duration of chelation therapy is around 4 years (1546.5 days), we can extrapolate that the paediatric patients enrolled in this registry well tolerated Exjade already.

In this study, one fatal case in a young patient (17 years-old) was reported (multi organ failure followed by acute chest syndrome) but it is doubtful (considering his medical history / SCD complications / polymedications). The incidence of adverse events suspected to be related to deferasirox was numerically lower in paediatric patients vs adult patients (3; 4.7%) and (7; 13.7%), respectively. The suspected adverse events in paediatric patients were AST increased, blood bilirubin increased, abdominal pain, abdominal pain upper, hypoesthesia, paraesthesia, rash (1; 1.6% each). No new safety concerns emerge from the data provided.

The overall safety profile was consistent with the known safety profile of Exjade and complications of underlying condition. Consequently, no amendment of SPC seems to be needed.

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 these both observational studies. Only descriptive data are available.

In the study AUS38, an apparent increase in serum ferritin between baseline and end of the study was observed in pediatric patients with SCD. The MAH suggests that patients were inadequately controlled for iron overload. The MAH should more discuss the value of maintaining deferasirox in this population.

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 AUS38 (SCD population), no new safety concerns emerge from the data provided.

The overall safety profile was consistent with the known safety profile of Exjade and complications of underlying condition. Consequently, no amendment of SPC seems to be needed at this stage.

☒ 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 AUS38

1- Study AUS38 is an observational study which is not designed to assess the efficacy of chelation therapy (in particular deferasirox). Although this study was not designed to assess efficacy (no efficacy in primary and secondary objectives) the apparent increase in serum ferritin between baseline and end of the study should be discussed (mean serum ferritin (SF) concentration from 2355.77 µg/L at baseline (n=44) and 2584.38 µg/L (n = 59) at the end of the study in pediatric patients). The MAH should comment.

2- Based on the data provided, it cannot be assessed if there is an impact of duration of therapy with Exjade in real life to hepatic/renal parameters in a specific category of patients. Therefore, the MAH should provide a table with the frequency of relative change from baseline to EOS for each hepatic (AST, ALT) and renal parameters (ClCr if available) by treatment duration in the paediatric population.

3- The MAH should review all paediatric cases of stroke under Exjade therapy.

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

MAH responses to Request for supplementary information

Question 1

Study AUS38 is an observational study which is not designed to assess the efficacy of chelation therapy (in particular deferasirox). Although this study was not designed to assess efficacy (no efficacy in primary and secondary objectives) the apparent increase in serum ferritin between baseline and end of the study should be discussed (mean serum ferritin (SF) concentration from 2355.77 µg/L at baseline (n=44) and 2584.38 µg/L (n = 59) at the end of the study in pediatric patients). The MAH should comment.

MAH's response

At baseline, the mean serum ferritin (SF) concentration was 2355.77 µg/L and the median SF value was 1830.00 µg/L (min: 140.0; max: 10054.0) in paediatric patients (n = 59); at the study end, it was 2584.38 µg/L and 1899.50 µg/L (min: 159.1; max: 8699.0)., respectively (n=44) ([Table 14.3-2.3a] of the Appendix 1: Statistical output for study CICL670AUS38 in eCTD sequence 0114, module 5.3.5.3).
The efficacy results in this study are not consistent with historical results reported from multiple other studies, including randomized well-controlled studies. In the extension phase of the registration study ICL670A109E1, when evaluating sickle cell disease patients with transfusional hemosiderosis who completed at least 4 years of deferasirox therapy, the median decrease in serum ferritin from baseline to the end of study was -590.7 µg/L [95% CI: -1571.2;-245.2] and the median relative change was -27.8% [95% CI:-44.7,-5.1].
The reason(s) for the inconsistent efficacy results are not known, however there are a number of possible explanations. One important limitation of this study was related to its design as an observational study which did not impose a particular treatment or drug, predefined treatment groups or clinical or laboratory assessments other than those required for disease management. Moreover, some of the serum ferritin values were missing, making the interpretation of the findings challenging.

Additionally, monitoring of compliance was not mandated in this observational study. Noncompliance to therapy has been a well-documented reason for serum ferritin increases (Alvarez, 2009).

In addition, several factors specific to sickle cell anaemia may increase serum ferritin concentration, most notably sickle cell pain crisis, including acute chest syndrome, inflammation and infection. Notably, in this observational study, pain crisis, acute chest syndrome and infections were observed in 44 (68.8%), 28 (43.8%) and 27 (42.2%) paediatric patients respectively. In this observational study, it is not possible to determine whether serum ferritin values recorded were influenced by factors other than iron status.

In summary, considering the inflammatory nature of the disease and limitations of observational studies, it is not possible to determine specifically why the serum ferritin changes over time were not consistent with results from most other studies.

Assessment of the MAH's response

Although this study was not designed to assess efficacy, it was requested to the MAH to discuss the apparent increase in serum ferritin between baseline and end of the study in pediatric patients.

In this AUS38 study, the severity of iron overload of this population at the baseline and at the end of the study is not documented. In addition, several limitations relative to observational studies (SF values missing, monitoring of compliance no mandatory, difference of clinical practice) were identified by the MAH. As a result, no conclusion about the efficacy of deferasirox could be drawn in pediatric population. Although some questions were raised about the efficacy in some pediatric patients treated for sickle cell disease, this unexpected result seems to be related to a specific population with inflammatory conditions who cannot, at this stage, be identified.

Question 2

Based on the data provided, it cannot be assessed if there is an impact of duration of therapy with Exjade in real life to hepatic/renal parameters in a specific category of patients. Therefore, the MAH should provide a table with the frequency of relative change from baseline to EOS for each hepatic (AST, ALT) and renal parameters (ClCr if available) by treatment duration in the paediatric population.

MAH's response

Additional analyses were performed for the hepatic and renal parameters and can be found in [Appendix 1]. In this observational study, data were collected every 6 months. The changes in ALT, AST and serum creatinine observed during the study were single measurements and were not confirmed consecutively and therefore cannot be directly compared to other studies where notable values were defined as confirmed laboratory changes (2 consecutive values, at least 7 days apart).
Within the study population being analyzed, 27 (42.2 %) paediatric patients had ALT values ≤ULN (Upper Limit Of Normal) and 35 (54.7%) patients had single ALT value greater than the ULN and less than 5 times the ULN during the 3-year observation period (see Table 2-1). Notably, of those 35 patients with post baseline value ALT value greater than the ULN and less than 5 times the ULN, there were 10 (28.6%) patients who entered the study with ALT levels above the ULN. One (1.6%) patient had a single post-baseline increase in ALT above 10 times the upper limit of normal and greater than 2 times above the baseline. Notably, this patient had a medical history of chronic pancreatitis, two episodes of acute pancreatitis as well as endoscopic retrograde cholangiopancreatography with stent placement.

Table 2-1 Shift table of ALT from baseline to highest post baseline category (Full analysis set) in patients <18 years of age treated with deferasirox

Highest post baseline	n (%)	Baseline ≤ULN n (%)	Baseline >ULN - ≤5xULN n (%)	Baseline >5xULN - ≤10xULN n (%)	Baseline >10xULN n (%)	Baseline Missing n (%)
≤ULN	27 (42.2)	23 (85.2)	3 (11.1)	0 (0.0)	0 (0.0)	1 (3.7)
>ULN - ≤5xULN	35 (54.7)	25 (71.4)	10 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)
>5xULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>10xULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>5xULN and >2xBL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>10xULN and >2xBL	1 (1.6)	0 (0.0)	1 (100)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	1 (1.6)	1 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	64 (100)	49 (76.6)	14 (21.9)	0 (0.0)	0 (0.0)	1 (1.6)

Source: [Table 14.3-2.5a of Appendix 1]

Abbreviations: BL: baseline, ULN: upper limit of the normal range

During the study, there were 63 (98.4%) paediatric patients who experienced a single increase in aspartate aminotransferase (AST) value greater than the ULN and less than 5 times the ULN (see Table 2-2). Notably, the majority of these patients, 54 (84.5%) had AST levels above the ULN at the baseline and only few, 8 (12.7%) had their AST ≤ ULN.

Table 2-2 Shift table of AST from baseline to highest post baseline category (Full analysis set) in patients <18 years of age treated with deferasirox

Highest post baseline	n (%)	Baseline ≤ULN n (%)	Baseline >ULN - ≤5xULN n (%)	Baseline >5xULN - ≤10xULN n (%)	Baseline >10xULN n (%)	Baseline Missing n (%)
≤ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>ULN - ≤5xULN	63 (98.4)	8 (12.7)	54 (85.7)	0 (0.0)	0 (0.0)	1 (1.6)
>5xULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>10xULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>5xULN and >2xBL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>10xULN and >2xBL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	1 (1.6)	0 (0.0)	1 (100)	0 (0.0)	0 (0.0)	0 (0.0)
Total	64 (100)	8 (12.5)	55 (85.9)	0 (0.0)	0 (0.0)	1 (1.6)

Source: [Table 14.3-2.6a of Appendix 1]

Abbreviations: BL: baseline, ULN: upper limit of the normal range

Data on creatinine clearance have not been collected in study CICL670AUS38. Within this registry, 39 (60.9%) patients had a serum creatinine value ≤ULN and 20 (31.3%) patients experienced a single value increase above the ULN (see Table 2-3). Of those, 19 (95%) had serum creatinine ≤ULN and one had >ULN at the baseline. Only 4 (6.3%) patients had a single serum creatinine increase of 33% and above ULN.

Table 2-3 Shift table of serum creatinine from baseline to highest post baseline category (Full analysis set) in patients <18 years of age treated with deferasirox

Highest post baseline		Baseline		
	n (%)	≤ULN n (%)	>ULN n (%)	Missing n (%)
≤ULN	39 (60.9)	39 (100)	0 (0.0)	0 (0.0)
>ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>33% increased from BL	20 (31.3)	19 (95.0)	1 (5.0)	0 (0.0)
>ULN and >33% increased from BL	4 (6.3)	4 (100)	0 (0.0)	0 (0.0)
Missing	1 (1.6)	1 (100)	0 (0.0)	0 (0.0)
Total	64 (100)	63 (98.4)	1 (1.6)	0 (0.0)

Source: [Table 14.3-2.7a of Appendix 1]

Abbreviations: BL: baseline, ULN: upper limit of the normal range

Approximately one third of paediatric patients (22; 34.4%) receiving deferasirox, were treated with hydroxyurea concomitantly [Table 14.2-1.1.1 of Appendix 1]. Of note, hydroxyurea may cause temporary impairment of renal tubular function accompanied by elevations in serum uric acid, blood urea nitrogen, and creatinine levels. Elevation of hepatic enzymes has also been reported in patients receiving hydroxyurea. Furthermore, some paediatric patients were also receiving acetaminophen (as Panadeine – combination of paracetamol and codeine (13; 20.3%), or paracetamol alone (11; 17.2%) and ibuprofen (16, 25%) which are known to cause abnormal liver enzymes levels.
It is also important to highlight that several paediatric patients receiving deferasirox were concomitantly treated with amoxicillin (6; 9.4%), penicillin (9; 14.1%) and phenoxymethylpenicillin (19; 29.7%) all of which may negatively affects the renal function too.
Lastly, the renal abnormalities are commonly seen in patients with sickle cell disease due to crises of vascular obstruction resulting from sickled red blood cells. Considering the aforementioned confounding factors, the assessment of the effect of deferasirox on liver enzymes and serum creatinine is rather challenging and may not be conclusive.

Assessment of the MAH's response

The MAH did not provide a table with the frequency of relative change from baseline to EOS for hepatic parameters (AST, ALT) by treatment duration. Moreover, only serum creatinine was provided instead of creatinine clearance. Also, the MAH did not provide them by treatment duration as requested by the CHMP. Of note, approximately one third of patient< 18 years-old with serum creatinine value ≤ ULN (19 of 64 patients) experienced increased of serum creatinine >33% from baseline.
Therefore, based on the data provided by the MAH, it still cannot be assessed if there is an impact of duration of therapy with Exjade on real life to hepatic/renal parameters in pediatric population.

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 (specifically for renal and hepatic parameters) 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 clarified.
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.

Issue partially addressed.

Question 3

The MAH should review all paediatric cases of stroke under Exjade therapy.

MAH's response

During the observation period, no adult patients treated with deferasirox experienced a stroke. The only stroke cases on adults were on subjects that were not treated with deferasirox.
However, ten stroke events occurred in paediatric patients treated with deferasirox during the observation period.
A total of 4 pediatric patients experienced 6 stroke events *while* receiving deferasirox at the time of the event (subject IDs highlighted in dark grey in the table below). One patient had a transient ischemic attack (TIA) and one patient experienced a possible cerebrovascular event (not specified) (highlighted in light grey in the table below). All these were documented in the clinical database of the study and reported as serious adverse events (SAE) in the Novartis safety database (ARGUS). None of these cases were assessed by the investigators as suspected to be related to the study drug. The summary narratives of the stroke cases are outlined below. The full details are provided in [Appendix 2].
A detailed review of all stroke cases, which occurred during the observation period ('Follow up visit 1, 2, 3, 4, 5 and 10'), is presented in the table below.

Table 2-4 Detailed review of all stroke cases

Subject ID No.	Subject details	Stroke Date	Details	Comments
Paediatric patients				
45/5	9/F/BL	29Aug2011 11Oct2012 02Mar2013	Ischemic stroke -frontal Ischemic stroke - occipital Ischemic stroke - parietal	PHHO2011US14988 PHHY2012US067575 PHHY2013US054017
73/24	7/M/BL	29Apr2012	Ischemic stroke - frontal	PHHO2012US006907
84/6	3/F/BL	24Mar2014	Ischemic strokes – frontal and parietal	PHHY2014US037098
46/6	17/M/BL	25Jul2013	Ischemic stroke - frontal	PHHO2013US011076
73/18	15/F/BL	12Jun2011	Ischemic stroke – frontal	PHHO2011US10997: Event reported as transient ischemic attack
73/38	13/F/OT	28Nov2011	Ischemic stroke – unknown	PHHY2014US017485: Event reported as a possible 'cerebrovascular event'
4/18	3/M/BL	11Nov2011	Ischemic stroke – left frontal and left occipital	Stroke occurred prior to the initiation of treatment with deferasirox on 9-Jul-2013.
45/7	5/F/BL	13Apr2012	Ischemic stroke - parietal	Stroke occurred prior to the initiation of treatment with deferasirox on 5-Dec-2012
Paediatric patients not treated with deferasirox				
25/1	2/M/BL	NA	Ischemic stroke – multiple infarcts	Subject was not treated with deferasirox
25/16	3/M/BL	NA	Ischemic stroke – frontal	Subject was not treated with deferasirox
50/5	6/F/BL	NA	Hemorrhagic stroke – frontal, parietal, occipital and temporal	Subject was not treated with deferasirox
Adults not treated with deferasirox				
37/2	35/M/BL	12Aug2011	Ischemic stroke – frontal	Adult subject not treated with deferasirox.
37/14	36/F/BL	16Sep2012	Ischemic stroke – frontal	Adult subject not treated with deferasirox.

There were two paediatric patients under observation who experienced one stroke event each. Details of these cases were not collected, as these events 'stroke' occurred prior to the initiation of deferasirox treatment.

The 15 stroke cases previously quoted in the clinical overview occurred during the medical history of the pediatric patients ('No. of patients with stroke in the last 5 years') and not during the observation period ('Follow-up visit 1, 2, 3, 4, 5 and 10'). These 15 cases were documented at the baseline study visits of the patients. No details of the cases are available as the collection of such data was not mandated by the non-interventional study protocol.

Narratives

Reports:

A female child of 9 years, with a medical history of sickle cell anemia, moyamoya disease, seizure disorder, chronic transfusions and left parietal stroke (first stroke in year 2005 prior to treatment start on 18-Jan-2011), experienced 3 events of ischemic stroke on day 223, day 632, and day 774 after start treatment with deferasirox. All 3 events of the stroke were confirmed by magnetic resonance imaging (MRI) and magnetic resonance angiogram (MRA) or MRI only, involving various regions of the brain. The outcome of one event was not reported. The second event was reported as improving and third one was reported as complete recovery. During the third event, the patients underwent a planned left hemisphere revascularization procedure to treat moyamoya disease.

The causality for all 3 events of stroke was assessed by the investigator as not suspected to be related to deferasirox.

Report

A 16-year-old female adolescent, with a medical history of sickle cell anemia, silent myocardial infarct and stroke, on day 635 after start treatment with deferasirox developed acute pyelonephritis and transient ischemic attack (TIA) requiring hospitalization. On a brain computed tomography (CT) scan, evidence of remote infarct was observed. The patient underwent an elective right sided revascularization procedure with indirect anastomosis and dural inversion. Treatment with study medication was continued unchanged. The investigator assessed the event of TIA and acute pyelonephritis as not suspected to be related to study medication. The outcome of the event TIA was reported as recovered with sequelae. The event acute pyelonephritis was completely resolved.

Report

A male child of 8 years, with a medical history of sickle cell anemia, allergy, cerebrovascular accident (unknown date of first stroke) and moyamoya disease, on day 577 after start treatment with deferasirox patient developed left-sided weakness and aphasia and was hospitalized. On MRI, evidence of an acute ischemic infarctions to the right perirolandic region and right anterior frontal lobe were observed. The outcome of the event was not reported. The investigator assessed the event of stroke as not suspected to be related to study medication.

Report

A 13-year-old female adolescent with no medical history and no concomitant medications received deferasirox on an unknown date. During the study, the patient was hospitalized for observation for a possible cerebrovascular event (not specified). On the same day, the outcome of the event was reported as recovered. The investigator assessed the event as nonserious and the causality for the event was assessed as not suspected to deferasirox by the investigator.

Report

A female child of 6 years, with a medical history of sickle cell anemia, moyamoya disease and iron overload, experienced a left frontal and parietal ischemic stroke (unknown date). No concomitant medications were reported with the exception of ibuprofen.

On day 647 after start treatment with deferasirox for iron overload, the patient developed right-sided facial weakness and asymmetry, and right hemiparesis (no movement right arm/leg). On MRI and MRA, evidence of ischemia and acute infarction involving the left parietal region (territory of the posterior division middle cerebral artery) were observed. The investigator assessed the event of stroke as not suspected to be related to study medication.

The outcome of stroke was reported as condition improving.

Report

A patient, receiving deferasirox, with a medical history of sickle cell anemia was enrolled in the study when he was 17 years old. Prior to the enrollment, the patient had a history of stroke; the date and details of the first stroke are unknown. On day 1,893 after start treatment with deferasirox the patient was hospitalized with cholelithiasis, acute chest syndrome and septic shock. At the time of hospitalization the patient was 19 years of age. Bi-frontal cerebral hypodensity and bi-frontal cerebral infarcts (ischemic stroke) with significant edema were observed on CT scan of the head and the patient underwent two decompressive craniotomies. Subsequently the patient died due to acute chest syndrome, multiple organ failure, acute respiratory distress, septic shock, encephalopathy and acute renal failure. The investigator assessed the events as not suspected to be related to study medication.

MAH's conclusions

In this observational study, all 6 stroke events experienced by the 4 pediatric patients while on deferasirox treatment were ischemic in nature. These findings are not unexpected as the highest incidence of first infarction is observed in children, with the incidence thereafter decreasing between the ages of 20 and 29 years. The sickled red cells can aggregate into large masses which obstruct blood vessels and result in damage to tissues and organs. These so called 'sickle cell crises' can affect a variety of organs including cerebrovascular injury, stroke and seizures. Risk factors associated with ischemic strokes include prior TIA, low steady-state hemoglobin concentration, rate of, and recent episode of acute chest syndrome and elevated systolic blood pressure (Ohene-Frempong K, 1998).
Notably, out of the patients who experienced stroke while on deferasirox treatment, 3 patients had a history of previous stroke, one patient had a history of stroke and moyamoya disease and one patient who experienced TIA also had a history of stoke. It is important to highlight that the children with stroke are at increased risk of recurrent stroke (28%) whereas children with stroke and moyamoya are at increased risk of recurrent TIA and stroke (58%), despite treatment with chronic transfusion (Strouse JJ, 2011). In this observational study, one of the patients who had previous stroke and moyamoya disease experienced 3 events of stroke.
Neurologic complications are a major cause of morbidity and mortality in sickle cell disease. Children and adults with sickle cell anemia have a high prevalence (4.01%) and incidence (0.61 per 100 patient-years) of cerebrovascular accidents. Multiple clinical and genetic associations have been identified with increased risk of stroke in this complex disease.

Assessment of the MAH's response

Ten stroke events occurred in 8 pediatric patients treated with deferasirox during the observation period. Two were excluded from the analysis due to the occurrence prior to the initiation of Exjade. Of the 6 remaining paediatric patients, 4 experienced 6 stroke events while receiving Exjade, one patient had a transient ischemic attack and one patient experienced a possible cerebrovascular event. None of these cases were assessed by the investigators as suspected to be related to the study drug.
Based on the data provided, the role of Exjade is doubtful due to the time to onset [223-1893 days], medical history of stroke (5 of 6 patients) and the underlying disease (SCD).
No action is required based on these data.

Issue addressed

5. CHMP overall updated conclusion and recommendation

Efficacy

The AUS38 study was not designed to assess efficacy. Several limitations relative to observational studies (SF values missing, monitoring of compliance no mandatory, difference of clinical practice) were identified by the MAH. As a result, no conclusion about the efficacy of deferasirox could be drawn in pediatric population. Although some questions were raised about the efficacy in some pediatric patients treated for sickle cell disease, this unexpected result seems to be related to a specific population with inflammatory conditions who cannot, at this stage, be identified. Therefore, no action is required based on these data.

Safety

In the study AUS38 (SCD population), no unexpected events were observed from the data provided.
After reviewing the data on stroke events in paediatric population, the role of Exjade is doubtful due to the time to onset [223-1893 days], medical history of stroke (5 of 6 patients) and the underlying disease (SCD). Therefore, no action is required based on these data.

However, based on the data provided by the MAH, it still cannot be assessed if there is an impact of duration of therapy with Exjade on real life to hepatic/renal parameters in pediatric population.

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 (specifically for renal and hepatic parameters) 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.