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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/P46/060.1

Note

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

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1. Introduction

On 11 December 2014, the MAH has submitted fifteen completed paediatric studies for EXJADE, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. The 15 clinical study reports are issued from local studies with deferasirox that enrolled pediatric patients (defined as patients aged < 18 years): four interventional and eleven observational studies.

Responses to the list of questions of the updated assessment report are provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the 15 local studies described in this assessment report are stand-alone studies. A line listing of all the concerned studies is annexed in section 2.3.1.

2.2. Information on the pharmaceutical formulation used in studies

Exjade is brand name for deferasirox presented as dispersible tablets in 3 doses strengths: 125, 250 and 500mg. The investigational drug was available as tablets at dosage strengths of 125 mg, 250 mg and 500 mg.

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 (\geq 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 (\geq 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 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 non-transfusion-dependent thalassaemia syndromes.

The MAH submitted the final reports for the fifteen clinical studies (4 interventional and 11 observational studies) and a clinical overview of these studies.

These 15 studies were performed for multiple purposes, for example to better characterize the prevalence and the magnitude of iron overload in a specific country or a region, or to confirm the

safety and efficacy of deferasirox in some local patient populations. The following table summarizes the main characteristics of each study.

List of four interventional studies							
Study number	Study tittle	Design	Objectives	Paediatric exposure			
CICL670AAU01	A study of Magnetic Resonance Imaging Assessment of Cardiac and Liver Iron Load in patients with Haemoglobinopathies, Myelodysplastic Syndromes (MDS) or other anaemias treated with Exjade® (deferasirox) - The MILE Study	Two-cohort single arm open label phase IV All patients received Exjade®.	Change in cardiac iron overload as measured by MRI T2*	53 patients were enrolled including 5 patients aged 16-17 years.			
CICL670ABR03	Deferasirox for the treatment of transfusional iron overload in sickle cell anemia: a 2-year prospective study	Open-label, non- comparative non- randomized single center phase IV All patients received Exjade.	Efficacy and safety of deferasirox in SCD patients	31 patients were enrolled including 13 patients aged <20 years.			
CICL670ARU01	Open-label multicenter study of Exjade ® (deferasirox) for treatment of transfusional iron overload in MDS, thalassemia and other anemia patients	Open-label, non- randomized, multi- center phase IV All patients received Exjade.	Efficacy and safety of deferasirox in patients with MDS, thalassemia and other anemias	111 patients were enrolled including 30 paediatric patients (2-12 years) and 13 paediatric patients (13-17 years).			
CICL670AUS04	An open label trial evaluating cardiac T2* in β-thalassemia patients on deferasirox (ICL670) treatment for 18 months	Open-label, single arm, multicenter phase IV All patients received Exjade.	Change in cardiac iron as measured by MRI T2* in β - Thalassemia patients with evidence of cardiac iron overload and normal cardiac function	28 patients were enrolled including 5 paediatric patients (10-16 years).			

List of eleven observational studies

Study number	Study tittle	Design	Objectives	Paediatric exposure
CICL670A1401	Drug Use Observational Study Protocol on Exjade® Tablet for Suspension (From the start of administration to one year thereafter) EXJ-1-01 in all patients who started treatment with Exjade no later than 31 Jan 2012	PMS	To confirm the safety and efficacy under actual use conditions	EXJ-1-01: 3372 patients enrolled until Oct 2012 (20 - 70 years and older) including 57 patients < 20 years, of which 40 < 15 years (1.60% of the study population). EXJ-2-01: 145 subjects were enrolled including
	EXJ-2-01 in patients who used Exjade on a long-term basis			3 patients < 20 years, with only 1 patient < 15 years
CICL670A2418	Complications in Patients with SCD and Utilization of ICT: A Retrospective Medical Records Review	Retrospective cohort Study 78 patients received Exjade®.	Retrospective chart review of SCD complications	254 patients were reviewed (16 years and older)
CICL670ABR01	Study RE-LA-TH: A Retrospective epidemiologic study of Latin-American subjects with transfusional	International, multicenter, cross- sectional, retrospective epidemiological	To investigate the magnitude of the problem and patterns of care of iron overload in	975 patients were enrolled (2 – 93 years)

	hemosiderosis	study	Latin America	
		60 patients (13.6%) received Exjade.		
CICL670ADE04	Exjade: Post-Marketing Surveillance Study on Tolerability and Efficiency of Exjade® (Deferasirox) in Patients with Transfusion- dependent Iron Overload and with Prior Chelation Therapy	Prospective uncontrolled open-labelled, multicenter observational study All patients received Exjade®.	To evaluate the tolerability and efficacy of deferasirox in patients previously treated with Desferal®	109 patients were enrolled (3 – 88 years), including 8 paediatric patients (<16 years).
CICL670ADE05	Extend: Post- Marketing Surveillance Study on Tolerability and Efficiency of Exjade® (Deferasirox) in Patients with first Treatment of Transfusion-dependent Iron Overload	Prospective uncontrolled open-labelled, multicenter observational study All patients received Exiade.	To evaluate the tolerability and efficacy of deferasirox in iron chelation naïve patients	226 patients were enrolled (3 – 91 years), including 3 paediatric patients (<16years).
CICL670AGR01	A non-intervENtional obsERvational study assessinG safetY of deferasirox in patients with transfusional iron overload: the 'ENERGY' study	single arm, openlabel, prospective, non-interventional observational study All patients received Exjade.	To assess the safety of deferasirox in patients with chronic iron overload related to blood transfusions applied for the treatment of anemias	230 patients were enrolled $(3 - 91)$ years), including 24 paediatric patients <16 years ($8 \ge 2 - 6$ years, $9 \ge 6 - 12$ years and $7 \ge 12 - 16$ years).
CICL670AIC02	Assessing Iron Overload in Transfusion- dependent patients by MRI in Latin America (ASIMILA Study)	open,multicenter, observational study	To determine the prevalence and the severity of liver and cardiac IOL in Transfusion dependent patients	212 patients were enrolled (10 – 80 years), including 29 paediatric patients (<18 years).
CICL670AKR01	Regulatory Postmarketing Surveillance Report for Exjade® Tablet	open-label, multicenter, single-arm observational study	To identify unknown AEs, incidence of AEs and factors that may affect the safety or efficacy of Exjade® under the real-life conditions in its approved indications.	1579 patients were enrolled, including 209 patients (≥ 2 - < 12 years) .
CICL670ASE01	Observational study Evaluating safety and efficacy of EXjade® (deferasirox) in TRansfusional dependent Anemias - EXTRA	Open-label, nonrandomized observational study	To evaluate efficacy and safety in patients treated with Exjade® in transfusional dependent anemias.	61 patients were enrolled, including 1 paediatric patient < 18 years (10 years).
CICL670ATR01	A prospective, noninterventional Multicenter multinational registry of anemia patients requiring chronic transfusional therapy who are at risk for transfusional hemosiderosis	Non-interventional observational study No study-specific treatment administered	To study the magnitude of the problem of IOL in Turkey, Australia, Korea, Taiwan, Russia, Israel, Thailand, Malaysia, Hong Kong, China, Singapore, gaining insight about this condition and the	564 patients were enrolled, including 57 paediatric patients aged <18 years (10.1% of the overall population).

			patterns of care use of ICT for transfusion dependent anemias in this region.	
CICL670ATW01	Single-arm, Observational, Safety Evaluation of Exjade in Patients with Transfusion Hemosiderosis	Multi-center, open label, non- comparative, observational study	To evaluate the safety profile of Exjade® in the treatment of thalassemia for 2 years.	127 patients were enrolled (2 – 69 years), including 8 children (2 -<12 years), 47 adolescents (12 - <20 years).

2.3.2. Clinical studies

CHMP's comment

As a general comment, the investigation of paediatric use was not a primary objective of these studies and the majority of them did not analyze the paediatric patients separately.

Various parameters were used in the interventional or non-interventional studies to measure efficacy, such as change from baseline in regular time intervals in cardiac iron overload (by using myocardial MRI T2*), cardiac function endpoints (LVEF), liver iron concentration (by using liver MRI T2*), serum ferritin, transferrin saturation. These are acceptable variables. Of note, 2 studies did not report any efficacy information (CICL670ABR01 and CICL670ATR01).

As a reminder, these clinical study reports were submitted in the context of article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

Therefore, the lack of a clear description of patient exposure and dose interruption data by age group in order to compare paediatric and adult population renders difficult an assessment of the benefit risk for the pediatric population.

2.3.2.1. Interventional studies

2.3.2.1.1. Study number CICL670AAU01: A study of Magnetic Resonance Imaging Assessment of Cardiac and Liver Iron Load in patients with Haemoglobinopathies, Myelodysplastic Syndromes (MDS) or other anaemias treated with Exjade® (deferasirox) - The MILE Study

Description

Two-cohort single arm open label study over a 53 week period, to evaluate the change in cardiac iron load measured by MRI T2* sequence technique. This study was performed in Australia.

Period of study: 28-Nov-2007 (First patient enrolled) to 08-Sep-2011 (Last patient completed).

<u>Methods</u>

Objectives

<u>Primary objectives of this trial</u> are to evaluate the change in cardiac iron load and cardiac ejection fraction by MRI after 53 weeks of Exjade treatment in the following:

 \bullet Transfused patients with haemoglobinopathies (thalassaemia-major and SCD) and a serum ferritin of > 500 µg/L.

• Myelodysplasic Syndrome (MDS) and other rare anaemias (e.g. Myeloproliferative Disease (MPD), Diamond-blackfan anaemia [DBA]) patients who demonstrate evidence of transfusional iron overload by a serum ferritin of > 1,000 μ g/L.

Primary Endpoints

The primary endpoint, change in cardiac iron load from baseline to 53 weeks, was defined as the log ratio of cardiac T2* at 53 weeks to baseline, In (T2*53/T2*0).

Secondary objectives of this trial are to evaluate the following:

• Change in LVEF values, left ventricular volume and mass measured by cardiac MRI from baseline values after 53 weeks of Exjade treatment.

• Change in cardiac T2* from baseline to 53 weeks in the MDS and other anaemias subgroup, compared to the thalassaemia subgroup.

• Changes in serum ferritin from baseline values to 53 weeks.

• Changes in Liver Iron Concentration (LIC) by MRI of the Proton Transverse Relaxation Rate (R2-MRI) from baseline values to 53 weeks.

• The relationship between the dosing regimen of Exjade and changes in cardiac T2* and LIC R2 MRI.

• Change in Blood Magnetic Susceptibility Blood magnetic susceptibility (BMS), from baseline to 53 weeks of Exjade.

• The safety and tolerability of Exjade therapy from baseline to 53 weeks.

Secondary Endpoints

• Left ventricular size and function

• serum ferritin, liver iron concentration, blood magnetic susceptibility, ALT,AST and serum creatinine.

Study design

Safety and tolerability of Exjade in the study population were captured at the clinic visits by assessments which consisted of collecting all AEs, serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of haematology, blood chemistry and urine performed at (study centre / central laboratory), electrocardiograms (ECGs), echocardiograms, regular assessments of vital signs, physical condition and body weight and documentation of concomitant medications/therapies. The Study Management Committee also reviewed the safety data regularly.

Study population /Sample size

The study population consisted of 53 patients with transfusional iron overload enrolled in two cohorts, of patients with either haemoglobinopathy (thalassaemia-major or SCD) or other inherited or acquired anaemia (MDS, MPD, DBA and other rare anaemias) who required regular blood cell transfusions. The originally planned sample size of 120-150 was revised after a planned interim analysis.

Overall, patients had a mean age of 36.3 years, and most patients were female (60.4%) and Caucasian (67.9%). The remaining patients were classified as Oriental (17.0%) or Other (15.1%). Proportions of patients in terms of gender and race for the 2 largest groups, patients with thalassemia major/SCD (n=42) or MDS/anaemia (n=9), were similar.

Table 14.1.2: Demography Population: All enrolled

Characteristic	Cateogry	Summary	Overall (N=53)	Th-maj/SCD (N=42)	MDS/Anaemia (N=9)	BMT (N=1)	DBA (N=1)
Age (years)		N	53	42	9	1	1
		Mean (SD)	36.3 (18.57)	29.6 (11.74)	68.0 (8.54)	55.0 (-)	16.0 (-)
		Median	30.0	28.0	65.0	55.0	16.0
		Min, Max	(16, 79)	(16, 75)	(53, 79)	(55, 55)	(16, 16)
Gender	Female	n (%)	32 (60.4%)	26 (61.9%)	5 (55.6%)	1 (100.0%)	0 (0.0%)
	Male	n (%)	21 (39.6%)	16 (38.1%)	4 (44.4%)	0 (0.0%)	1 (100.0%)
Race	Caucasian	n (%)	36 (67.9%)	25 (59.5%)	9 (100.0%)	1 (100.0%)	1 (100.0%)
	Black	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Aboriginal	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Oriental	n (%)	9 (17.0%)	9 (21.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Other	n (%)	8 (15.1%)	8 (19.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Child bearing potential	Yes	n (%)	27 (84.4%)	26 (100.0%)	1 (20.0%)	0 (0.0%)	0 (0.0%)
	No	n (%)	5 (15.6%)	0 (0.0%)	4 (80.0%)	1 (100.0%)	0 (0.0%)
Pregnancy test result	Positive	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Negative	n (%)	27 (100.0%)	25 (100.0%)	2 (100.0%)	0 (0.0%)	0 (0.0%)

Changes in planned analysis

During the course of the study, analyses were undertaken for three conferences. For these presentations, it was required to <u>create four cohorts</u>, rather than the original two. Although the protocol planned to recruit patients into two cohorts, each with various disease substates, the expectation was that there would be multiple patients within each of the disease substates providing a homogenous estimate of treatment effect for each of the two planned cohorts. However, at the end of recruitment there were two patients, one DBA and one bone marrow transplantation (BMT), who, if included in the corresponding main cohort would severely distort the estimates of treatment effect. It was determined for clinical reasons that these two patients would remain in their own single patient cohorts.

Treatments

Exjade was supplied as 125 mg, 250 mg and 500 mg tablets which were dispersed.

For patients who were not receiving Exjade prior to study entry, the recommended initial daily dose was 20 mg/kg/day. A starting dose at 30 mg/kg/day could be allowed for some patients, depending on the therapeutic goals or transfusional iron intake. Initial dose of 10 mg/kg/day for 2 weeks (followed by 20 mg/kg/day) was allowed in order to reduce the risk of gastrointestinal disturbances, especially in the elderly.

Patients were allowed to enter the study if already receiving Exjade at doses ranging from 20 to 40 mg/kg/day. For patients who were receiving Exjade prior to study entry and were not adequately controlled with doses of 30 mg/kg (e.g. serum ferritin levels persistently above 2500 µg/L for at least 3 months and not showing a decreasing trend over time), escalation to 40 mg/kg could be considered at study entry. Patients experiencing AEs due to Exjade treatment were permitted dose adjustments in order to continue on the drug. These dose adjustments could be interruptions in dosing and/or reductions in the dose being administered. Refer to the study protocol for the guidelines for dose reductions and delays. Doses above 40 mg/kg/day were not allowed in this study.

Outcomes/endpoints

Protocol Deviations were detected during the first 30 months of the study (total = 28; low starting dose = 14; concomitant illnesses = 12; lab value out of range at enrolment = 1; concomitant use of investigational drug = 1).

	Overall	Th-maj/SCD	MDS/Anaemia	BMT	DBA
Patients					
Screened	63	51	10	1	1
Exposed	53	42	9	1	1
Completed	43	37	5	1	0
Discontinued	10	5	4	0	1
Main cause of discontinuation					
Death	0	0	0	0	0
Adverse event(s)	3	1	2	0	0
Lack of efficacy	1	1	0	0	0
Protocol violation(s)	3	1	1	0	1
Administrative reasons	2	2	0	0	0

Table 10-1	Patient disposition – all enrolled
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Statistical Methods

All analyses were planned to be performed for all subjects in the full analysis population, irrespective of the disease state and were to be repeated by patient cohort (transfused patients with haemoglobinopathies and other anaemias). Descriptive statistics (for continuous variables, namely n, mean, median, minimum, maximum and SD) or frequencies and percentages (for categorical variables) were planned to be presented by visit for all efficacy and safety variables assessed in this study (except AEs). AEs were planned to be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class and also by preferred term as then number (and percentage) of patients experiencing at least one event in each category during the study.

A detailed Statistical Analysis Plan (SAP) was prepared prior to inspection of any data by the biostatistician and prior to database lock in which all aspects of data analysis were defined in detail.

Safety population

All patients who received at least one dose of study drug were included in the safety population. The safety population were used to produce all listings, summaries and analyses of safety data.

Recruitment/ Number analysed

The Main Criteria for Inclusion in this trial:

Patient \geq 18 years and weighing > 40 kg

Male or female patient with haemoglobinopathy (thalassaemia-major or SCD) or other anaemia (inherited or acquired; e.g. MDS, MPD, DBA and other rare anaemias) who required regular blood cell transfusions.

Lifetime minimum of > 20 units of packed red blood cell transfusions

• Serum ferritin > 500 μ g/L for patients with haemoglobinopathies (thalassaemia-major or SCD) or serum ferritin > 1,000 μ g/L for patients with any other congenital or acquired anaemia (e.g. MDS/MPD, Diamond-blackfan anaemia)

• Normal or minimally abnormal cardiac function (New York Heart Association [NYHA] Class 1, LVEF ≥ 50% measured by echocardiography or nuclear medicine gated pool blood scan [GBPS])

• Female patients who had reached menarche and who were sexually active must have been using an effective method of contraception, or must have undergone clinically documented total hysterectomy and/or ovariectomy, or tubal ligation and have a negative pregnancy test.

The inclusion criteria changes to with amendment 1 of the protocol (released 270CT2010).

Male or female haemoglobinopathy, MDS or post BMT patient >= 16 years and weighing > 40 kg.

Results

Efficacy results

For the primary endpoint of change in cardiac iron load from baseline to end of study, results were significant (p = 0.002) for all patients in the full analysis set.

No specific analyses of the efficacy in paediatric patients have been conducted.

Safety results (safety population)

Forty-seven (88.7%) patients in the Safety population experienced at least one treatmentemergent AE during the study and nine (17.0%) patients reported serious AEs. Three (5.7%) patients discontinued the study because of AEs.

A total of 284 treatment-emergent AEs were recorded throughout the study period, **77 of which were considered treatment related**. Fourteen of the AEs were recorded as serious (in 9 patients), 12 were recorded as severe serious AEs, 7 were severe nonserious AEs and 4 AEs resulted in permanent discontinuation of the study drug (in 4 patients).

Table 14.3.3: Summary of treatment emergent adverse events by system organ class and preferred term Population: Safety Set

System Organ Class Preferred Term name	Overall (N=53)	Th-maj/SCD (N=42)	MDS/Anaemia (N=9)	BMT (N=1)	DBA (N=1)
Subjects with at least one AE	47 (88.7%)	37 (88.1%)	9 (100.0%)	1 (100.0%)	0 (0.0%)
GASTROINTESTINAL DISORDERS	34 (64.2%)	24 (57.1%)	9 (100.0%)	1 (100.0%)	0 (0.0%)
DIARRHOEA	15 (28.3%)	10 (23.8%)	5 (55.6%)	0 (0.0%)	0 (0.0%)
NAUSEA	11 (20.8%)	7 (16.7%)	4 (44.4%)	0 (0.0%)	0 (0.0%)
ABDOMINAL PAIN	8 (15.1%)	4 (9.5%)	4 (44.4%)	0 (0.0%)	0 (0.0%)
ABDOMINAL PAIN UPPER	6 (11.3%)	6 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CONSTIPATION	5 (9.4%)	4 (9.5%)	1 (11.1%)	0 (0.0%)	0 (0.0%)
VOMITING	5 (9.4%)	3 (7.1%)	2 (22.2%)	0 (0.0%)	0 (0.0%)
ABDOMINAL DISTENSION	3 (5.7%)	2 (4.8%)	1 (11.1%)	0 (0.0%)	0 (0.0%)
ABDOMINAL DISCOMFORT	1 (1.9%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ABDOMINAL PAIN LOWER	1 (1.9%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
BOWEL MOVEMENT IRREGULARITY	1 (1.9%)	0 (0.0%)	1 (11.1%)	0 (0.0%)	0 (0.0%)
DRY MOUTH	1 (1.9%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)
DUODENAL ULCER	1 (1.9%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DYSPEPSIA	1 (1.9%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

The most common preferred terms (\geq 10%) included diarrhoea in 15 (28.3%), patients, upper respiratory tract infection in 14 (26.4%) patients, nausea in 11 (20.8%), patients, blood creatinine increased in 11 (20.8%) patients, abdominal pain in 8 (15.1%), patients, ALT increased in 8 (15.1%) patients, back pain in 7 (13.2%) patients, abdominal pain upper in 6 (11.3%) patients, and urinary tract infection in 6 (11.3%), patients. Rates of treatment-emergent AEs by patient group were 88.1% in patients with, thalassemia major/SCD, 100% in patients with MDS/anaemia or Bone marrow transplantation (BMT), and none in the 1 patient with Diamond-blackfan anaemia (DBA).

Table 14.3.3: Summary of treatment emergent adverse events by system organ class and preferred term Population: Safety Set

System Organ Class Preferred Term name	Overall (N=53)	Th-maj/SCD (N=42)	MDS/Anaemia (N=9)	BMT (N=1)	DBA (N=1)
EPIGASTRIC DISCOMFORT	1 (1.9%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GASTRITIS ATROPHIC	1 (1.9%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MOUTH HAEMORRHAGE	1 (1.9%)	0 (0.0%)	1 (11.1%)	0 (0.0%)	0 (0.0%)
MOUTH ULCERATION	1 (1.9%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
RECTAL HAEMORRHAGE	1 (1.9%)	0 (0.0%)	1 (11.1%)	0 (0.0%)	0 (0.0%)
INFECTIONS AND INFESTATIONS	33 (62.3%)	27 (64.3%)	6 (66.7%)	0 (0.0%)	0 (0.0%)
UPPER RESPIRATORY TRACT INFECTION	14 (26.4%)	13 (31.0%)	1 (11.1%)	0 (0.0%)	0 (0.0%)
URINARY TRACT INFECTION	6 (11.3%)	4 (9.5%)	2 (22.2%)	0 (0.0%)	0 (0.0%)
NASOPHARYNGITIS	3 (5.7%)	2 (4.8%)	1 (11.1%)	0 (0.0%)	0 (0.0%)
GASTROENTERITIS	2 (3.8%)	2 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INFLUENZA	2 (3.8%)	2 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
LOWER RESPIRATORY TRACT INFECTION	2 (3.8%)	1 (2.4%)	1 (11.1%)	0 (0.0%)	0 (0.0%)
SINUSITIS	2 (3.8%)	2 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TONSILLITIS	2 (3.8%)	2 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
VIRAL INFECTION	2 (3.8%)	1 (2.4%)	1 (11.1%)	0 (0.0%)	0 (0.0%)

The most common treatment-emergent AEs in terms of System Organ Class were gastrointestinal disorders in 34 (64.2%) patients, infections and infestations in 33 (62.3%) patients, investigations in 21 (39.6%) patients, general disorders and administrative site conditions in 14 (26.4%) patients, musculoskeletal and connective tissue disorders in 12 (22.6%) patients, and respiratory, thoracic and mediastinal disorders in 11 (20.8%) patients.

There were 6 treatment-related treatment-emergent AEs that occurred in \geq 5% of patients overall. These were diarrhoea in 14 patients (26.4%), nausea in 8 patients (15.1%), blood creatinine increased in 8 patients (15.1%), rash in 4 patients (7.5%), abdominal pain in 3 patients (5.7%), and vomiting in 3 patients (5.7%).

Table 14.3.9: Summary of treatment related, treatment emergent adverse events of moderate severity, by system organ class and preferred term Population: Safety Set

System Organ Class Preferred Term name	Overall (N=53)	Th-maj/SCD (N=42)	MDS/Anaemia (N=9)	BMT (N=1)	DBA (N=1)
Subjects with at least one AE	12 (22.6%)	8 (19.0%)	4 (44.4%)	0 (0.0%)	0 (0.0%)
GASTROINTESTINAL DISORDERS	7 (13.2%)	4 (9.5%)	3 (33.3%)	0 (0.0%)	0 (0.0%)
DIARRHOEA	6 (11.3%)	3 (7.1%)	3 (33.3%)	0 (0.0%)	0 (0.0%)
ABDOMINAL PAIN	1 (1.9%)	0 (0.0%)	1 (11.1%)	0 (0.0%)	0 (0.0%)
ABDOMINAL PAIN UPPER	1 (1.9%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
VOMITING	1 (1.9%)	0 (0.0%)	1 (11.1%)	0 (0.0%)	0 (0.0%)
INVESTIGATIONS	4 (7.5%)	3 (7.1%)	1 (11.1%)	0 (0.0%)	0 (0.0%)
ALANINE AMINOTRANSFERASE INCREASED	2 (3.8%)	2 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
BLOOD ALKALINE PHOSPHATASE INCREASED	1 (1.9%)	0 (0.0%)	1 (11.1%)	0 (0.0%)	0 (0.0%)
SERUM FERRITIN DECREASED	1 (1.9%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (3.8%)	1 (2.4%)	1 (11.1%)	0 (0.0%)	0 (0.0%)
RASH	2 (3.8%)	1 (2.4%)	1 (11.1%)	0 (0.0%)	0 (0.0%)

The majority of AEs were mild, with 88.7% of patients experiencing mild, 49.1% experiencing moderate, and 15.1% experiencing severe AEs. No severe AEs occurred in more than 2 patients (3.8%), and the only severe AE occurring in 2 patients was diarrhoea. One moderate AE (diarrhoea) occurred in 6 patients (11.3%), and no other moderate AE occurred in more than 3 patients (5.7%). These moderate and severe events of diarrhoea were considered to be related to study treatment.

Table 14.3.10: Summary of severe treatment related, treatment emergent adverse events, by system organ class and preferred term Population: Safety Set

System Organ Class	Overall	Th-maj/SCD	MDS/Anaemia	BMT	DBA
Preferred Term name	(N=53)	(N=42)	(N=9)	(N=1)	(N=1)
Subjects with at least one $\ensuremath{\mathtt{A}}\xspace$	2 (3.8%)	0 (0.0%)	2 (22.2%)	0 (0.0%)	0 (0.0%)
GASTROINTESTINAL DISORDERS	2 (3.8%)	0 (0.0%)	2 (22.2%)	0 (0.0%)	0 (0.0%)
DIARRHOEA	2 (3.8%)	0 (0.0%)	2 (22.2%)	0 (0.0%)	0 (0.0%)
NAUSEA	1 (1.9%)	0 (0.0%)	1 (11.1%)	0 (0.0%)	0 (0.0%)
METABOLISM AND NUTRITION DISORDERS	1 (1.9%)	0 (0.0%)	1 (11.1%)	0 (0.0%)	0 (0.0%)
DEHYDRATION	1 (1.9%)	0 (0.0%)	1 (11.1%)	0 (0.0%)	0 (0.0%)
HYPOKALAEMIA	1 (1.9%)	0 (0.0%)	1 (11.1%)	0 (0.0%)	0 (0.0%)

Seven patients (13.2%) experienced SAEs. Of these patients, 4 had thalassemia major/SCD and 3 had MDS/anaemia. No SAE occurred in more than 1 patient. SAEs included diarrhoea, rectal haemorrhage, vomiting, chest pain, pyrexia, sickle cell anaemia with crisis, lobar pneumonia, neutropenic sepsis, wrist fracture, bone pain, musculoskeletal pain, mania, and renal colic. **Diarrhoea and vomiting were the only SAEs considered related to treatment.**

Table 14.3.12: Summary of treament related, treatment emergent serious adverse events by system organ class and preferred term Population: Safety Set

System Organ Class Preferred Term name	Overall (N=53)	Th-maj/SCD (N=42)	MDS/Anaemia (N=9)	BMT (N=1)	DBA (N=1)
Subjects with at least one AE	1 (1.9%)	0 (0.0%)	1 (11.1%)	0 (0.0%)	0 (0.0%)
GASTROINTESTINAL DISORDERS	1 (1.9%)	0 (0.0%)	1 (11.1%) 1 (11.1%)	0 (0.0%)	0 (0.0%)
VOMITING	1 (1.9%)	0 (0.0%)	1 (11.1%)	0 (0.0%)	0 (0.0%)

Discussion on clinical aspects

In this study ten patients discontinued prematurely; 4 withdrew due to AEs (2 AEs of diarrhoea and 2 AEs of blood creatinine increased), 3 due to protocol violations, 2 due to withdrawal of consent, and 1 due to lack of efficacy. Seven patients experienced SAEs during the study (diarrhoea, rectal haemorrhage, vomiting, chest pain, pyrexia, sickle cell anaemia with crisis, lobar pneumonia, neutropenic sepsis, wrist fracture, bone pain, musculoskeletal pain, mania, and renal colic; all n=1 event each). All patients had a complete recovery from those events. Two of the cases had suspected relationship to study drug (diarrhoea and vomiting).

No statistically significant changes were seen over time in serum creatinine and AST levels for the overall patient population, nor when patients were stratified by subgroup (haemoglobinopathy/MDS). ALT was the only parameter that showed a statistically significant change over time (i.e. reduction), and that was limited to the MDS subgroup (p=0.01).

The change in safety markers for patients receiving a mean dose of Exjade >30mg/kg/day did not show statistical difference when End of Study values were compared with baseline (p=0.4, 0.2 and 0.7 for serum creatinine, ALT and AST respectively; results extracted from the statistical model based on the overall patient population).

CHMP's comments:

Change in cardiac iron load from baseline to end of study was provided for the overall population (pediatric and adult).

No specific analyses of the efficacy in paediatric patients have been conducted.

The assessment of drug safety was only a secondary objective in this study. Initially the patients < 18 years old were not included in this study but with an amendment, **5 patients** \ge **16 years old** were included but the safety data are presented globally, without details on the pediatric patients.

Research in the line listing find 5 patients <18 years old: 1 adolescent with beta thalassemia, 1 adolescent with thalassemia Major, 1 adolescent with SCD and 1 adolescent with DBA. All of them received Deferasirox before entry in this study. Research in the adverse event listing find 4 drug related adverse events for these patients: 1 gastrointestinal disorder (vomiting), 2 renal and urinary disorders (hematuria) and 1 musculoskeletal and connective tissue disorder (back pain). All of these DRAE are mild.

2.3.2.1.2. Study number CICL670ABR03: Deferasirox for the treatment of transfusional iron overload in sickle cell anemia: a 2-year prospective study

Description: An open-label, non-comparative trial Phase IV with deferasirox in patients with SCD and transfusional iron overload was carried out in one center in Brazil.

Period of study: 24/08/2007 (First patient enrolled) to 15/08/2008 (Last patient completed)

Methods

Objectives: Objectives of this trial were to evaluate the iron overload status, before and after two year-treatment with deferasirox, using liver iron concentration by magnetic resonance imaging (MRI) hepatic, MRI cardiac (Cardiac T2*, ms), serum ferritin (SF, μg/L), and to evaluate the <u>safety and</u> tolerability of deferasirox. Safety was evaluated on a monthly basis according to the incidence and type of adverse events and measurement of laboratory parameters, including serum creatinine and liver enzyme levels.

Study design: This trial was a unicenter, prospective, non-randomized, open-label phase IV study of 1 year duration in Brazil.

Study population /Sample size: Male and female patients aged >2 years with SCD and transfusional iron overload were enrolled. Iron overload was defined as the use of \geq 20 units of RBC units and/or SF levels \geq 1000 µg/L confirmed by \geq measurements during the previous 6 months of enrollment. Patients with active hepatits B and C were excluded from participating in this study.

31 pediatric (age >2y) and adult (age < 65y) patients with SCD and iron overload were enrolled. 13 patients <20 years old (In Table 1 Patient demographic and selected clinical parameters).

Table 1. Patient demographic and selected clinical parameters (n=31)

Pacient Characteristic	n (%)
Age (years)	
Mean ± SD	26.9 ± 12.5
Median (range)	25 (9-49)
Age group, n	
< 20 years	13 (41.9)
20 to 30 years	8 (25.8)
> 30 years	10 (32.3)
Female, n (%)	26 (84)
Afrodescendant	28 (90)

Treatments

All eligible patients who had been previously treated with deferoxamine discontinued this drug and entered a 7-day washout period. All patients, regardless of their baseline LIC, commenced deferasirox at a dose of 20 mg/kg/day. Dose adjustments of 5-10 mg/kg/day (range of 5 g/kg/day up to 30 mg/kg/day), which were possible only after 12 weeks of study treatment, were done every 3 months if necessary.

The dose of deferasirox was reduced by one dose level and not re-escalated for patients 15 years of age and older if serum creatinine increased >33% above baseline on two consecutive occasions. Deferasirox was interrupted for moderate or severe skin rash and reinstituted at half the initial dose, and dose reescalation was permitted. Treatment was continued for 2 years and was only interrupted at the discretion of the investigator for intercurrent illness or adverse events.

Outcomes/endpoints

The main efficacy endpoint were the change in LIC and serum ferritin from baseline assessed at 2-yr period. The assessment of safety was based mainly on the frequency of adverse events and on the number of laboratory values that fell outside the predetermined ranges.

Statistical Methods

Testing for statistics significance for differences between baseline and end-of-study for each treatment group was performed using Student's *t*-test. Using a two-sided test, P-values <0.05 were considered to be statistically significant.

Results

A total of 31 pediatric (age >2y) and adult (age < 65y) patients with SCD and iron overload, defined as the use of \ge 20 units of RBC units and/or two SF levels \ge 1000 µg/L during the 6 months preceding enrollment, received starting dose of 20mg/kg/day of deferasirox. Two patients discontinued treatment at 8 and 9 months, due to pregnancy and moving to other city, respectively. One patient died at 18 months due to pulmonary infection and hemorrhagic stroke. Deferasirox was interrupted in 3 (10.3%) patients due to confirmed serum ferritin levels <500 µg/L. Twenty-five patients completed 2-year treatment. Mean ± SD and median (range) age 26.9 ± 12.5y and 25.0y (9-49), <20 years 13 patients 41.9% 20 to 30 8 patients 25.8%.

Efficacy results

No specific analyses of the efficacy in paediatric patients have been conducted.

Reduction in body iron in SCD patients from a BL mean SF of 2344.5 ng/ml to 2113 ng/ml at 12 months and 1986.3 ng/ml at 24 months.

Safety results (safety population)

The most common drug-related Adverse Events were mild, transient diarrhea (7 patients), headache (7 patients), nausea (5 patients) and vomiting (3 patients). Maculo-papular skin rash and serum creatinine increases upper limit of normal were observed in 2 (6.5%) patients. Three patients (9.5%) had two consecutive increases in serum creatinine that were both >33% above baseline and above the upper limit of normal (ULN); there were no progressive increases. **This adverse event occurred most frequently in those patients older than 25 years of age** and all of them responded to dose reduction with stabilization or normalization of this parameter. Two patients (6.5%) experience two consecutive serum creatinine increases >33% above baseline that exceeded the (ULN), never ≥ 2 times the ULN. No patient experienced progressive increases in serum creatinine or renal failure. In both these individuals, deferasirox was interrupted and, after normalization of the serum creatinine level that occurred in both patients the drug was rechallenged without recurrence of the creatinine increase. Reversible increases in alanine aminotransferase (ALT) were seen in 2 (6.5%) patients. No patient experience ALT levels >3x ULN. Reversible increases in alanine aminotransferase (ALT) were seen in 2 (6.5%) patients. No patient experience ALT levels >3x ULN.

Table 3. Adverse events

Adverse	Frequency,		Severity, n (%)	
Event	n (%)	Mild	Moderate	Severe
Diarrhea	7 (22.6)	7 (22,6)	0 (0,0)	0 (0,0)
Headache	7 (22.6)	6 (19,4)	1 (3,2)	0 (0,0)
Nausea	5 (16.1)	5 (16,1)	0 (0,0)	0 (0,0)
Creatinine increased	2 (6.5)	1 (3,2)	1 (3,2)	0 (0,0)
Dizziness and/or sonolence	3 (9.7)	3 (9,7)	0 (0,0)	0 (0,0)
Maculo- papular skin rash	2 (6.5)	1 (3,2)	0 (0,0)	0 (0,0)

Discussion on clinical aspects

According to the MAH, this trial confirms that deferasirox is effective in reducing body iron burden in transfused patients with SCD, well tolerated in pediatric and adult patients and with a clinically manageable safety profile. Over 2 years of deferasirox treatment showed no evidence of progressive increases in serum creatinine in patients with SCA, who have tendency to develop progressive renal disease. No severe adverse event occurred in this study.

CHMP's comments:

The mean reduction SF is provided for the overall population (ie pediatric and adult). No specific analyses of the efficacy in paediatric patients have been conducted.

In this trial, pediatric population >2 years old was included but the number of children in this study is not clear. The adverse events are not distributed by age but seems to be more frequent in the oldest patients >25 years.

2.3.2.1.3. Study number CICL670ARU01: Open-label multi-center study of Exjade (deferasirox) for treatment of transfusional iron overload in MDS, thalassemia and other anemia patients.

Description: Open-label multi-center prospective non randomized study. Reference therapy was not used.

Methods:

Objectives:

- **Primary objective** was to assess the degree of reduction of the ferritin level during Exjade therapy in the patients with transfusion iron overload.
- Secondary objectives:

1. Assess the clinical implications of post-transfusion iron overload in the patients suffering from Myelodysplastic syndrome, thalassemia, and other kinds of anemia

2. Assess the target lesions when there is an occurrence of evident post-transfusion iron overload

3. Assess acceptability/safety of Exjade by observing the patients suffering from the post transfusion iron overload;

Study design: Open-label multicenter non randomized study

Study population/sample size: Adult patients suffering from Myelodysplastic Syndrome (presenting with low or intermediate-1 IPSS risk) and patients aged >2 y.o with thalassemia or rare anemias (Diamond-Blackfan anemia, Fanconi's anemia, Sideroblastic anemia, Red cell aplasia). A target patient group consisting of 120 people was formed.

Treatments: All the patients participating in the investigation were prescribed Exjade® (deferasirox). A combination of dispersible tablets 125, 250 and 500mg was used to adjust the dosage. Patients got the drug in the initial dosage depending on the extent of iron overload and transfusion therapy:

- 30 mg/kg/ day provided that the Ferritin level >2500 µg/l and more than 4 transfusions of a donor erythrocytes is received per month
- 10 mg/kg/day provided that the Ferritin level <1500 µg/l and less than 2 transfusions of a donor erythrocytes is received per month
- 20 mg/kg/day in other cases

The treatment was administered as recommended by the marketing authorization. The treatment duration was 12 months.

Outcomes/endpoints for safety assessment:

Safety assessment was carried out by means of monitoring and registration of all the adverse events and serious adverse events (SAE) (together with assessment of severity level and relation to the study drug intake), cardiac function assessment, regular clinical and biochemical blood and urine analyses, vital signs assessment and physical examination including weight measurements and functional class determination.

Regular monitoring of clinical and biochemical blood and urine analyses, creatinine clearance, procedures to assess cardiac function (ECG, Echo-CG), US of the abdominal cavity organs, an optician and an ENT doctor examination, audiogram were all conducted in the local laboratories of the research centers.

All the SAEs, AEs, the results of the cardiac function assessment, as well as all the results of laboratory tests were registered in the patients' case report forms (CRF).

Statistical methods: For evaluation of safety parameters, taking into consideration the noncomparative nature of the investigation, the frequency of AEs is presented in a descriptive way, and the analysis of variance (ANOVA) is applied to the results of biochemical analysis.

Results:

Recruitment/Number analyzed: 111 patients were recruited for the investigation, 3 were excluded for protocol violations, then 108 were analyzed.

Baseline data: All the patients were divided into a group of adults (>18 y.o.), a group of adolescents (from 13 to 17 y.o.) and a group of children (from 2 to 12 y.o.). The teenage group was 13 patients; children-30 patients.

- In children from 2 to 12 years old, there were 13 boys and 17 girls, and the median of age was 6 years old. The primary diagnosis was Beta-thalassemia (15 patients), Diamond-Blackfan anemia (8 patients), genetic megalocytic hemolytic anemia (1), Fanconi's anemia (1), myelodysplastic syndrome (1), genetic dyserythropoietic anemia (1), pure red cell aplasia (1), acquired aplastic anemia (1) and hemolytic anemia with abnormal HbC (1). While the children group anamnesis data was being analyzed, it was made clear that 20 out of 30 children had already been taking chelating therapy. Most of them had been taking Desferal®-14 (46,7%) and 6 (20%) children had been taking Exjade®.
- In adolescents (from 13 to 17 years old), there were 4 boys and 9 girls, with an average age of 15 years old. The principal diagnosis was: Beta-thalassemia (4 patients), Diamond-Blackfan anemia (3 patients), genetic megalocytic hemolytic anemia (2), Fanconi's anemia (1), myelodysplastic syndrome (1), hemoglobinopathiy (1), genetic hemolytic anemia (1). 10 (77%) out of 13 patients had been taking chelating therapy. 6(46%) patients had been taking Desferal®, 3 patients had been taking Exjade® and the last deferiprone.

The initial dose of Exjade, the patient exposure duration were not presented by age groups.

Efficacy results

No specific analyses of the efficacy in paediatric patients have been conducted.

Reduction in mean SF was reported for all patients from BL of 3837.2 ng/ml to 2269.2ng/ml at 12 months.

Safety results

Overall experience of adverse events: Data of 108 patients were used to conduct the statistical analysis. Adverse events were recorded with 85 patients (78.5%). 219 cases of adverse events development were detected with these patients. 23 (10.5%) cases of AEs were referred to as serious. The most frequent reasons for AEs development were the gastrointestinal tract disorders-35 cases (16%) and different infections-35 cases (16%). 23 (10.5%) cases of AEs developed as a result of a general disorder and laboratory data deviations. Less frequent were the blood and lymphatic system disorders 22 cases (10%).

Number and percentage of patients with AEs overall and by system organs

System organ class affected	219 (100%)
	22 (122)
Blood and lymphatic system disorders	22 (10%)
Cardiac disorders	13 (5,9%)
Ear and labyrinth disorders	5 (2,3%)
Eye disorders	5 (2,3%)
Gastrointestinal disorders	35 (16%)
General disorders	23 (10,5%)
Immune system disorders	8 (3,7%)
Infections and infestations	35 (16%)
Laboratory data deviations	23 (10,5%)
Metabolism and nutrition disorders	7 (3,2%)
Musculoskeletal and connective tissue disorders	1 (0,45%)
Neoplasms benign, malignant and unspecified	3 (1,4%)
Nervous system disorders	6 (2,7%)
Psychiatric disorders	2 (0,9%)
Mamma and reproductive system disorders	1 (0,45%)
Renal and urinary disorders	17 (7,8%)
Respiratory, thoracic and mediastinal disorders	6 (2,7%)
Skin and subcutaneous tissue disorders	2 (0,9%)
Vascular disorders	5 (2,3%)

The most frequent laboratory and clinical AEs against the background of the drug intake were the increase in transaminase level, hyperbilirubinemia-17 cases (7.8%), urinary tracts infections- 11 cases (5%), influenza symptoms appearance-11 cases (5%), sicchasia-9 cases (4.1%). The most frequent adverse events appearing against the background of Exjade treatment are gastrointestinal tract disorders (diarrhea, nausea, vomiting, pain in the stomach), hives sometimes together with liver transaminase rise, creatinine level in blood serum rise. The most of the adverse events are dosage connected.

- 2. **Deaths, other serious and significant adverse events:** Clinically relevant AEs were considered those which demanded the reduction of the investigational drug dosage or temporary/permanent discontinuation of the treatment. 23 (10.5%) cases AEs were considered serious, among them 10 (4.6%) cases resulted in death. Not a single fatal case of AEs development was connected with the investigational drug intake. The cause of deaths was :
 - myelodysplastic syndrome progression (3 cases).
 - transformation of myelodysplastic syndrome into acute leukemia with thrombocytopenia (1 case). This patient had experienced 2 significant AEs. One of them was erythema multiform of the 4th severity degree. The researcher deduced the connection between this AE and the study drug intake. This led to the Exjade therapy discontinuation and supplementary drug-induced therapy.
 - progression of a unspecified oncological disease (1). This patient had experienced one AEproteinuria of the first severity degree according to NCI CTC scale. This AE was not significant and didn't demand the study drug modification or supplementary drug-induced therapy.
 - acute coronary syndrome (1),
 - sudden death (1),

- disseminated intravascular coagulation (1),
- pulmonary embolism (1),
- pulmonary edema (1).

108 cases (49.3%) were referred to as clinically significant AEs and demanded the dosage reduction or temporary/constant discontinuation of its intake or supplementary therapy. In two cases (0.9%) researches made a decision to discontinue the patient's participation in the trial due to SAE development. Only in 1 case the patient discontinued the participation in the trial due to the clinically significant AE. The allergic reaction to the study drug which firstly resulted in the dose reduction but then led to complete termination of its use occurred only with 1 patient.

Number and percentage of patients with most frequent AEs

Number (%) of natients studied	108 (100%)	
Number (%) of patients with AFs	85 (78 7%)	
Number (70) of patients with ALS	11 010	
Most frequent AEs	overall – 219	
	cases (100%)	
Transminers and bilimbin land	17 (7.89/)	
Transminase and oniruom level	17 (7,8%)	
Increase	11 (59())	
Unnary tract infection	11 (5%)	
Flu-like symptoms	11 (5%)	
Sicchasia	9 (4,1%)	
Proteinuria	8 (3,7%)	
Allergic reactions	8 (3,7%)	
Diarrhea	8 (3,7%)	
Hyperglycaemia	7 (3,2%)	
Hypercreatininemia	6 (2,7%)	
Brochialis infection	5 (2,3%)	
Eye disorders	5 (2,3%)	
Abdominal pain	5 (2,3%)	
Ear infection	4 (1,8%)	
Febriculosity	4 (1,8%)	
ESR rising	4 (1,8%)	
Chronic kidney disease	4 (1,8%)	
Viral hepatitis	4 (1,8%)	
Myocardiodistrophy	4 (1.8%)	
Cardiac decompensation	4 (1,8%)	
Pneumonia	3 (1,4%)	
Anemia	3 (1,4%)	
Neoplasms benign	3 (1,4%)	
Bronchialis blocking	3 (1,4%)	
Glucose intolerance	3 (1,4%)	
Pharingitis	3 (1,4%)	
Varicella	3 (1,4%)	
Infectious rhinitis	3 (1,4%)	
General disorder	3 (1,4%)	

Serious adverse events

			Influence on the			
Name	Duration	Grade	study drug	Actions taken	Result	Bond
Ear infection	18	2	No	Hospitalization	Resolved	No
Pneumonia	86	2	No	Drug-induced therapy	Consequences	No
Aortic valve disorder	0	3	No	Hospitalization	Consequences	No
Flu-like semiotics	14	1	No	Hospitalization	Resolved	No
Acute coronary syndrome	0	4	No	Other	Death	No
DIC syndrome	17	4	No	Hospitalization	Death	No
Oxymortia	0	4	No	No	Death	No
Acute leukemia	1	4	No	Drug-induced therapy	Death	No
Thrombembolia	1	4	Discontinuation	Hospitalization	Death	No
Cerebrum neoplasm benign Cancer without primary	17	4	No	Hospitalization	Continuation	No
neoplasm, bone metastasis	0	4	No	Hospitalization	Death	No
Toxic hepatitis	8	4	Interruption	Hospitalization	Consequences	Yes
Vasovagal syncope	20	2	No	Hospitalization	Resolved	No
Thrombophlebitis, soft tissue						
infection	14	2	No	Drug-induced therapy	Resolved	No
Aortic valve disorder	0	3	No	Hospitalization	Consequences	No
Thrombocytopenia	1	4	No	Drug-induced therapy	Death	No
Toxic hepatitis	6	2	Interruption	No	Resolved	Yes
Cardiac decompensation	106	3	No	Other	Continuation	No
Acute leukemia	12	3	No	Hospitalization	Death	No
Pulmonary edema	0	4	Cessation	Drug-induced therapy	Death	No
Pneumonia	12	3	Cessation	Hospitalization	Resolved	No
General disorder, hypotension	30	3	No	Hospitalization	Resolved	No
Myelodysplastic Syndrome	48	4	No	Hospitalization	Death	No

- 3. Laboratory values: The analysis of the peripheral blood data the statistically relevant differences weren't discovered. The basic biochemical blood variables (ALT, AST, bilirubin, creatinine, glucose) were monitored as safety criteria on Visits. When conducting the analysis of variances (ANOVA) the statistically relevant variables weren't detected, except ALT level decrease. One of the reasons can be the patients with hepatic malfunction discontinued the participation in the study.
- 4. **Vital signs:** During the examinations weight, blood pressure, Respiration rate, Heart rate levels, temperature were measured. During the investigation and statistical analysis meaningful differences weren't detected.
- 5. **Other safety evaluations:** At the beginning and at the end of the investigational drug intake all the patients had the following instrumental tests conducted: X-ray examination of thoracic cage organs, US of abdominal cavity organs, ECG, EchoCG, audiographics. All the patients were examined by an optician and an ENT specialist on Visit 0 and Visit12. Clinically significant differences in the results weren't detected.

CHMP's comments:

The mean reduction SF is provided for the overall population (ie pediatric and adult). No specific analyses of the efficacy in paediatric patients have been conducted.

The assessment of drug safety was only a secondary objective in this study. Patients were divided into age groups (adults, adolescents and children) but the safety data are presented globally, without details on the pediatric patients. Adverse events were not differentiated from adverse drug reactions (ADR). We noticed that among the serious adverse events, the drug was interrupted in two cases of **toxic hepatitis** and a causal relationship was retained for these two cases; but we don't know whether these cases involved children or not.

2.3.2.1.4. Study number CICL670AUS04: An open label trial evaluating cardiac T2* in β -thalassemia patients on deferasirox (ICL670) treatment for 18 months

Description

A phase IV post marketing trial surveillance study was performed in United States. The study period is between 14-Feb-2006 (First patient enrolled) to 04-Nov-2009 (Last patient completed)

Methods

Objective(s)

The primary objectives of this study are:

In Core Study

To evaluate changes in cardiac iron as measured by MRI T2* from baseline to 25, 49, and 77 weeks of study in β -thalassemia patients with evidence of cardiac iron overload and normal cardiac function.

In Extension Phase To evaluate changes in cardiac iron as measured by MRI T2* from baseline to 101 weeks of study in β -thalassemia patients with evidence of cardiac iron overload and normal cardiac function

The Secondary Objectives of this study are:

In Core Study

To evaluate:

Safety and tolerability of deferasirox 30 - 40 mg/kg/day for up to 77 weeks

Changes in liver iron concentration as measured by MRI R2 or SQUID from baseline to 25, 49, and 77 weeks of study.

• Rates of change of cardiac and liver iron from baseline to 25, 49, and 77 weeks of therapy.

• Changes in ventricular ejection fraction as measured by MRI and echocardiography from baseline to 25, 49, and 77 weeks of study.

- Changes in serum ferritin from baseline through 25, 49, and 77 weeks of study.
- Changes in trough NTBI (LPI and DCI), serum iron, transferrin, and transferrin saturation.

• Whether changes in trough NTBI (LPI and DCI) or transferrin saturation correlate with changes in cardiac or liver iron.

• Compliance with use of deferasirox using pill counts at every visit.

In Extension Phase

To evaluate:

Safety and tolerability of deferasirox 30 - 40 mg/kg/day for up to 101 weeks.

Changes in liver iron concentration as measured by MRI R2 or SQUID from baseline to 101 weeks of study.

• Changes in ventricular ejection fraction as measured by MRI and echocardiography from baseline to 101 weeks of study.

• Changes in serum ferritin from baseline through 101 weeks of study.

Study design

Thirty patients with abnormal T2, but normal cardiac function were to be enrolled into an open-label, single-arm pilot trial. The screening period was to last up to 4 weeks. All patients were to initiate treatment with 30 mg/kg/day deferasirox for 77 weeks in the core study. Patients whose T2* had improved over the 18 months on the core study, but had not yet reached 20ms, may have continued on a 6-month extension phase.

Study population /Sample size

The total number of patients planned for this study was 30. The total number of patients recruited was 28. There were 28 patients in the intent-to-treat (ITT) population and 27 patients in the safety population. There were 22 patients in the completer population. Eleven of these patients formally continued in the extension phase (PT-Table 14.1-1.1). One patient enrolled in the extension phase discontinued participation early due to a withdrawn consent.

Demographic and background characteristics:

The mean (\pm SD) patient age was 22.6 (\pm 8.67) years, ranging from 10 to 44 years. Five patients were aged 10 to <16 years (17.9%).

Treatments

Dispersible tablets of the investigational agent, deferasirox were to be supplied in dosage strengths of 125mg, 250mg and 500mg per tablet. The starting dose chosen for all patients in this study was 30mg/kg/day. Patients who were currently on > 30 mg/kg/day of deferasirox could have continued on their pre-existing dose at study entry. Previous experience with deferasirox has shown that net negative iron excretion can occur at doses of 20 to 30 mg/kg/day. The mean dose of deferasirox taken over the 77 and 101-week (extension phase patients only) study periods was 30.87 mg/kg/day and 34.77 mg/kg/day, respectively.

• For daily doses of 1 to 3 g, the tablets should have been dispersed. Concomitant therapy with any other iron chelator was not allowed. All 27 patients indicated that they had been exposed to an iron chelating agent prior to the start of study drug; 26 patients (96.3%) had taken deferasirox mesilate before initiation of study treatment

Patients may have been withdrawn from the study prematurely for one of the following reasons : adverse event(s), abnormal laboratory value(s), abnormal test procedure result(s), unsatisfactory therapeutic effect, condition no longer requires treatment, protocol violation, subject withdrew consent, lost to follow-up, administrative problems, and death.

Any patient who discontinued study drug but refused to return for an end of study visit, must have been contacted for safety evaluations during the 4 weeks following the last dose of study drug.

In patients who developed a skin rash, the following dose adjustments should have been followed.

Recruitment/ Number analysed

There were 22 patients in the completer population. Eleven of these patients formally continued in the extension phase.

Of note, patients aged >10 years-old could be enrolled in this study. **The definition of the term 'pediatric' for enrollment and study conduct was in accordance with local legislation.**

Outcomes/endpoints

The primary efficacy endpoint was change in liver iron concentration at one year as assessed by liver biopsy.

Statistical Methods

Data were summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, drug exposure, and safety observations and measurements. Within group changes at each study visit versus baseline were tested using a Wilcoxon signed-rank statistic. This statistic tested a null hypothesis that the change from baseline was equal to 0.

Results

Efficacy results

No specific analyses of the efficacy in paediatric patients have been conducted.

There is an increase in cardiac MRI T2* from 9.92 msec at BL by 1.7 msec at week 25, 2.01 ms at week 49, and 2.18 msec at week 77.

Safety results (safety population)

Adverse events (AEs)

The overall incidence of adverse events by system organ class for the safety population is presented in Table 12-2. All remaining SOCs were reported at a frequency of less than 20%

	All Patients
	N=27
	n (%)
Patients with at least one AE	27 (100.0%)
Primary system organ class	
Gastrointestinal disorders	21 (77.8%)
Infections & infestations	19 (70.4%)
General disorders & administration site conditions	16 (59.3%)
Metabolism and nutrition disorders	13 (48.1%)
Respiratory, thoracic & mediastinal disorders	13 (48.1%)
Investigations	12 (44.4%)
Nervous system disorders	12 (44.4%)
Musculoskeletal & connective tissue disorders	11 (40.7%)
Skin & subcutaneous tissue disorders	11 (40.7%)
Injury, poisoning and procedural complications	7 (25.9%)
Cardiac disorders	5 (18.5%)
Renal & urinary disorders	4 (14.8%)
Vascular disorders	4 (14.8%)
Hepatobiliary disorders	3 (11.1%)
Psychiatric disorders	3 (11.1%)
Eye disorders	2 (7.4%)
Blood and lymphatic system disorders	1 (3.7%)
Congenital, familial and genetic disorders	1 (3.7%)
Ear and labyrinth disorders	1 (3.7%)
Immune system disorders	1 (3.7%)
Reproductive system & breast disorders	1 (3.7%)
Surgical and medical procedures	1 (3.7%)

Table 12-2 Incidence of AEs by primary system organ class (Safety Population)

Analysis of adverse events

Among the 27 patients receiving study drug, 3 (11.1%) had treatment-emergent AEs with a maximum severity of mild, 13 patients (48.1%) had a maximum severity of moderate, and 11 patients (40.7%) had a maximum severity of severe. Moderate or severe treatment emergent AEs experienced by > 5% of patients is shown in Table 12-4. The most frequently reported moderate/severe AEs were abdominal pain (29.6%), pyrexia (25.9%), nasopharyngitis (22.2%), headache (18.5%), nausea (18.5%), rash (18.5%), vitamin D deficiency (18.5%), vomiting (18.5%), cough (14.8%), blood creatinine increased (11.1%), dehydration (11.1%), hyperglycaemia (11.1%), hypotension (11.1%), and vitamin B complex deficiency (11.1%).

	All Patients N=27	
	Total	Moderate/
	n (%)	Severe
		n (%)
Patients with at least one AE	27 (100.0%)	24 (88.9%)
Preferred term		
Abdominal pain	10 (37.0%)	8 (29.6%)
Pyrexia	12 (44.4%)	7 (25.9%)
Nasopharyngitis	11 (40.7%)	6 (22.2%)
Headache	9 (33.3%)	5 (18.5%)
Nausea	16 (59.3%)	5 (18.5%)
Rash	7 (25.9%)	5 (18.5%)
Vitamin D deficiency	5 (18.5%)	5 (18.5%)
Vomiting	8 (29.6%)	5 (18.5%)
Cough	10 (37.0%)	4 (14.8%)
Blood creatinine increased	3 (11.1%)	3 (11.1%)
Dehydration	3 (11.1%)	3 (11.1%)
Hyperglycaemia	3 (11.1%)	3 (11.1%)
Hypotension	4 (14.8%)	3 (11.1%)
Vitamin B complex deficiency	3 (11.1%)	3 (11.1%)
Alanine aminortransferase increased	2 (7.4%)	2 (7.4%)
Aspartate aminotransferase increased	2 (7.4%)	2 (7.4%)
Carnitine deficiency	2 (7.4%)	2 (7.4%)
Ejection fraction decreased	2 (7.4%)	2 (7.4%)
Fatigue	9 (33.3%)	2 (7.4%)

Table 12-4Incidence of moderate or severe treatment-emergent
AEs by preferred term occurring in 5% or more of patients
(Safety Population)

Deaths, other serious adverse events and other significant adverse events

Of the 27 patients initiating treatment with deferasirox, 17 (63.0%) experienced at least one serious or significant AE. This total was comprised primarily by the number patients for whom an AE lead to a dose adjustment or temporary interruption of deferasirox (13/27, 48.1%). Eight patients (29.6%) experienced at least one non-fatal SAE, and 3 patients (11.8%) discontinued study drug permanently due to an AE of any type. Two patients discontinued because of adverse events (abnormal laboratory values and adverse events, including those of a serious nature) and ultimately died.

Table 12-5	Number of patients who died or experienced other serious or clinically significant adverse events (Safety Population)		
		All Patients	
		N=27	
		N (%)	
Serious or sigr	ificant AE	17 (63.0%)	
Death		0 (0.0%)	
Non-fatal SAE		8 (29.6%)	
Discontinued d	1 (3.7%)		
Discontinued due to non-serious AE*		3 (11.1%)	
AE leading to o temporary inte	dose adjustment or rruption	13 (48.1%)	

Two patient deaths occurred following withdrawal from the trial due to SAEs. One patient died due to congestive heart failure, and the other patient's death was secondary to multi-organ failure. These deaths, including the antecedent AEs, were not assessed as related to study drug.

Serious adverse events

Eight patients (29.6%) experienced one or more SAEs and include pyrexia (18.5%), abdominal pain (14.8%), vomiting (11.1%), dehydration (7.4%), and hypotension (7.4%).

	All Patients
Primary system organ class	N=27
Preferred term	n (%)
Patients with any SAE	8 (29.6%)
General disorders and administrative site conditions	
Pyrexia	5 (18.5%)
Gastrointestinal disorders	
Abdominal pain	4 (14.8%)
Vomiting	3 (11.1%)
Metabolism and nutritional disorders	
Dehydration	2 (7.4%)
Vascular disorders	. ,
Hypotension	2 (7.4%)

Table 12-6 Incidence of treatment-emergent SAEs occurring in 5% or more patients (Safety Population)

Study drug interruption/dose adjustment

Study drug interruptions and dose adjustments $$({\rm Safety\ Population})^1$$

		N=27
Any dose adjustment		
No	8	(29.6%)
Yes	19	(70.4%)
Reason for dose adjustment/interruption		
As per protocol		
Change in weight	2	(7.4%)
MRI	1	(3.7%)
Cardiac	0	(0.0%)
Increase in serum creatinine	0	(0.0%)
Serum ferritin <=500 ng/mL at 2 consecutive visits	2	(7.4%)
Skin rash	2	(7.4%)
Ejection Fraction	0	(0.0%)
AE	11	(40.7%)
Lack of efficacy	13	(48.1%)
Disease improvement under study	1	(3.7%)
Dosing error	4	(14.8%)

Analysis and discussion of deaths, other serious adverse events and other significant adverse events

While no patient discontinued the study due to death, two patients expired as a result of serious adverse events. The SAE leading to study drug discontinuation was not suspected as being related to deferasirox. Eight patients (29.6%) experienced SAEs, **but only 1 patient (3.7%) had one or more SAEs considered by the investigator to be study drug-related**. This patient had reported a moderate, suspected increase in blood creatinine on Day 174. Study drug was discontinued on Day 174 as well. He was hospitalized for heart failure apparently prior to this time (Day 162) and expired sometime on/after Day 174. The most frequent serious or significant adverse event was based on those occurrences leading to dose adjustments or temporary dose interruptions. This occurred in 48.1% of the treated patients.

Clinical laboratory evaluation

1- Hematology

There were two events reported as blood and lymphatic system disorders. A severe episode of disseminated intravascular coagulation was observed and another report was made for a case of severe Thrombocytopenia. These events were not suspected as related to deferasirox.

2 Clinical chemistry

AST

Seventeen out of the 27 treated patients had Grade 0 (normal) AST values at baseline. Ten patients had Grade 1 toxicity post-baseline. Grade 2 post-baseline toxicity was seen in 5 patients. Three patients experienced Grade 3 toxicity post-baseline Of these Grade 3 toxicities, 2 patients had abnormal toxicity at baseline and 1 patient had a normal value. No Grade 4 toxicity was reported post-baseline. Two patients reported an adverse event of increased AST: one case was moderate in severity and the other case was severe

ALT

Eight out of the 27 treated patients reported Grade 0 (normal) ALT values at baseline. Ten patients had Grade 1 toxicity post-baseline. Grade 2 post-baseline toxicity was seen in 6 patients. Five patients experienced Grade 3 or 4 toxicity post-baseline. Of these Grade 3/4 toxicities, all patients had abnormal (ie, not Grade 0) toxicity at baseline. An adverse event of increased ALT was reported by two patients. These episodes were moderate (n = 1) and severe (n = 1) in severity.

Creatinine Clearance

None of the 27 treated patients reported Grade 0 (normal) creatinine clearance values at baseline. Sixteen patients had Grade 1 toxicity post-baseline. Grade 2 post-baseline toxicity was seen in 10 patients. <u>One patient experienced Grade 3 toxicity post-baseline</u>. This patient had an abnormal value at baseline. No Grade 4 toxicity was reported post-baseline.

Creatinine

Twenty five out of the 27 treated patients reported Grade 0 (normal) creatinine values at baseline. One patient had Grade 1 toxicity post-baseline. Grade 2 post-baseline toxicity was seen in 1 patient. No patient experienced a Grade 3 or 4 toxicity post-baseline. Three patients reported an adverse event of increased creatinine. Two of these cases were moderate in severity and one patient had a severe event. One of these AEs was reported as a SAE.

Total Bilirubin

Four out of the 27 treated patients reported Grade 0 (normal) bilirubin values at baseline. Seven patients had Grade 1 toxicity post-baseline. Grade 2 post-baseline toxicity was seen in 10 patients. Six patients experienced Grade 3 toxicity post-baseline. Of these Grade 3 toxicities, all 6 patients had abnormal (ie, not Grade 0) values at baseline. No Grade 4 toxicity was reported post-baseline.

Other Serum Chemistry Values

Hyperglycemia was reported by three patients: 2 cases of moderate severity and 1 severe case. One of these events was reported as an SAE.

Ocular examinations

Ten (37.0%) out of 27 patients had a clinically significant abnormality at baseline. Twenty-six patients had missing data at the Week 77 assessment and thus, no inference could be made for this time point. This magnitude of missing data reflected the protocol requirement that the test was to be done postbaseline only if clinically indicated.

Summary of safety results

Of the 27 patients initiating treatment with deferasirox, 17 (63.0%) experienced at least one serious or significant AE. A total of 8 patients (29.6%) reported an SAE, of which only 1 patient had such an event suspected as being related to deferasirox. and 3 patients (11.8%) discontinued study drug permanently due to an AE of any type. Two patients discontinued because of adverse events (abnormal laboratory values and adverse events, including those of a serious nature) and ultimately died. The AEs leading to study drug discontinuation in these patients were judged not to be related to study drug.

One patient reported two severe SAEs related to blood disorders: disseminated intravascular coagulation and thrombocytopenia. Both of these events were not suspected as related to study drug. Three of the most commonly reported AEs suspected as related to study drug were gastrointestinal in nature: nausea (25.9%), diarrhea (18.5%), and abdominal pain (11.1%). In addition, deferasirox-related cases of increased serum creatinine levels were reported in 11.1% of the treated patients. Post-baseline Grade 3 and 4 laboratory toxicity was reported for a limited number of patients among four clinical chemistry laboratory parameters (AST, ALT, creatinine clearance, and total bilirubin). Laboratory SAEs were reported for increased creatinine (n=1) and hyperglycemia (n=1). Although a few laboratory parameters showed statistically significant changes from baseline at various study visits, none of these changes were of sufficient magnitude to warrant clinical concern. Four or fewer patients met critical threshold values for the majority of pre-specified safety alerts; the main alert noted was for patients experiencing at least one post-baseline value of AST or ALT >250 U/L. This occurred in 14.8% of the patients receiving study drug. A treatment-emergent occurrence of myocardial ischemia was seen for one patient.

CHMP's comments:

Change in cardiac overload measured by MRI T2* was provided for the overall population (pediatric and adult.

No specific analyses of the efficacy in paediatric patients have been conducted.

The assessment of drug safety was only a secondary objective in this study. Patients >10years old were included in this study but the safety data are presented globally, without details on the pediatric patients.

Research in the line listing find <u>5 patients <16 years old (between 10 and 14 years old):</u>, Research in the listing of the adverse events find 14 adverse events related to study medication for these patients: 7 Gastrointestinal disorders (nausea, vomiting, abdominal pain, diarrhea), 3 Renal, urinary and investigations disorders (abnormal urinalysis, increased Serum Creatinine, low Phosphorous), 1 Congenital, familial and genetic disorders (Fanconi's Syndrome), 1 Nervous system disorders (dizziness), 1 Metabolism and nutrition disorders (anorexia) and 1 General disorders (Fever). Two of these Drug Related Adverse Events are severe. Deferasirox, in this study, seems very well tolerated (only 1 patient had such an event suspected as being related to deferasirox and 3 patients (11.8%) discontinued study drug permanently due to an AE of any type) but in spite of a limited number of pediatric population (5 patients), we can find 14 DRAE which 2 severe in the adverse events listing. We also find a Fanconi Syndrome like a SDRAE in pediatric population, misclassified in congenital, familial and genetic disorders.

2.3.2.2. Observational studies

2.3.2.2.1. Study number CICL670A1401: Drug Use Observational Study Protocol on Exjade Tablet for suspension

Description:

This post-marketing surveillance study was performed in Japan between the market launch of Exjade in June 2008 and March 31, 2012 (to enroll patients who started treatment with Exjade no later than January 31, 2012) with two studies:

- EXJ-1-01: drug use observational study, all treated patients surveillance, with two follow up periods: from the start of treatment to 0.5 year with data recorded in the CRF01 and from 0.5 to 1 year with data recorded in the CRF02.
- EXJ-2-01 : special drug use observational study

Methods:

• EXJ-1-01

Objectives: to confirm the safety and efficacy under actual use conditions (All cases surveillance).

Study design: drug use observational study after the market launch of Exjade in Japan (June 16, 2008)

Study period: 01-Apr 2011 to 31-Mar-2012

Study population / Sample size: The number of patients was calculated to detect eye disorder and hearing impaired: the target sample size was 1000 subjects. Approximately 3000 subjects had been enrolled approximately 3 years after market launch to ensure that the case report forms (less than 6 months: CRF-01, from 0.5 to 1 year: CRF-02) would be collected from 1000 subjects.

• EXJ-2-01

Objectives: to confirm the safety and efficacy of long-term use under actual use conditions.

The special drug use observational study (EXJ-2-01) is being conducted in subjects who have been treated with Exjade starting in the drug use observational study (EXJ-1-01).

Treatment: The daily dose of Exjade was $14.3 \pm 5.38 \text{ mg/kg/day}$ (mean $\pm \text{ S.D. n=2170}$), showing that a high percentage of subjects received a lower dose than the approved dose of 20 mg/kg/day. The duration of treatment ranged extremely widely (mean $\pm \text{ S.D., 192.1} \pm 144.68 \text{ days, n=2454}$). Early discontinuation of treatment (less than 60 days from the initiation) was observed (27.33%), and long-term treatment (360 days or longer) was also observed (22.51 %).

Outcome: Description of adverse reactions (incidence, seriousness, timing, outcome and incidence by factor), Incidence of serious adverse reactions by factor, laboratory values, Adverse events of interest (renal impairment, hepatic impairment, gastrointestinal disorder, eye disorder, hearing impaired, decreased blood cells, leucocytoclastic vasculitis, hypersensitive reaction, agranulocytosis), ferritin levels.

Results:

EXJ-1-01:

Recruitment/number analyzed: Case composition in the drug use observational study:



A total of 3372 patients were enrolled, 2588 collected case report forms (CRF), but only CRF02 for 51 patients (excluded), therefore 2537 CRF analyzed: 2 subjects who were not treated, 12 subjects who could not be assessed for adverse events, and 17 subjects who were enrolled more than once were excluded, and the remaining **2506 subjects were included in the safety analysis: 2506 CRF01 and 1106 CRF02.**

Number of children: Children aged under 15 years accounted for 1.60% of the population = 40 patients, without information on the therapeutic indication.

Efficacy results

No specific analyses of the efficacy in paediatric patients have been conducted.

In general, treatment with Exjade resulted in a reduction in mean ferritin levels, despite large variability (or wide S.D.).

After treatment with Exjade, the ferritin levels decreased in subjects without transfusion, but slightly increased in those with transfusion.

Safety results

The incidence of adverse reactions was significantly lower in children aged under 15 years than in adults aged 15 years and older (22.50% versus 50.43%, p=0.0006). Furthermore, the incidence was the lowest at 28.07% in subjects aged under 20 years.

For the serious adverse reactions: the incidence of serious adverse reactions significantly increased with age (p=0.0054). The incidence of serious adverse reactions was not increased in children: 2.50% in children less than 15 years and 11.56% for patients aged 15 years and older. The incidence of serious adverse reactions was at 3.51% in patients aged under 20 years.

A total of 15 adverse reactions were reported in 9 of 40 children. These adverse reactions included diarrhea (4 cases), renal impairment (3), nausea (2), abdominal pain (2), liver disorder, ALT increased, AST increased, and blood creatinine increased (1 case each). The adverse reactions in children were renal impairment, hepatic impairment, and gastrointestinal disorder, which were also common in adults, with no specific adverse reaction in children.

While the exact cause of the lower incidence of adverse reactions in children is unknown, it may be explained by their inability to express their subjective symptoms.

The dose in children was 17.2 ± 6.40 mg/kg (mean \pm S.D.) and slightly higher than the mean dose (14.3 mg/kg) in the entire population, but the dose was not correlated with the incidence of adverse reactions. The mean body weight was 22.6 kg in children and 54.2 kg in adults, indicating that the approximate daily dose was 388.72 and 755.06 mg, respectively. Therefore, the lower total daily exposure in children than in adults may have resulted in the lower incidence of adverse reactions in children even though the mean dose was slightly higher in children.

The adverse events of interest (renal impairment, hepatic impairment, and gastrointestinal disorder, Eye disorder and hearing impaired, decreased blood cells and agranulocytosis, as well as hypersensitivity and leucocytoclastic vasculitis) were not shown by age.

<u>EXJ-2-01</u>

Recruitment/number analysed

As of October 31, 2012, 583 subjects have been enrolled in the special drug use observational study following 1-year treatment in the drug use observational study (EXJ-1-01). CRFs were collected from 155 of the 583 subjects. Of the 155 subjects from whom the CRFs were collected, **145 subjects were included in safety analysis**, excluding a total of 10 subjects: 9 subjects excluded from safety analysis in the drug use observational study and 1 subject who could not be enrolled.

Data from 142 CRF-01 (second year), 53 CRF-02 (third year), and 1 CRF-03 (fourth year) were tabulated.

Number of children: 1 patient aged under 15 years (0,69%) and 3 patients aged less than 20 years (2.07%).

Efficacy results

No specific analyses of the efficacy in paediatric patients have been conducted.

According to the MAH, a greater reduction in the ferritin levels was observed in the special drug use observational study than in the drug use observational study, indicating that the efficacy was highlighted due to the increased exposure after long-term treatment.

Safety results

Adverse reactions: none in patients under 15 years and one ADR for patients under 20 years

The serious adverse reactions and the adverse events of interest were not detailed by age.

CHMP's comments:

The mean reduction SF is provided for the overall population (ie pediatric and adult). No specific analyses of the efficacy in paediatric patients have been conducted.

Children under 15 account for only 1.60% of the studied population (40 cases).

Pediatric safety data in these 40 patients did not found unexpected adverse effects or more frequent adverse effects than in adults. Although the number of patients has been calculated to detect eye or ear disorders, the adverse effects of interest and the serious adverse reactions were not shown by age.

2.3.2.2. Study number CICL670A2418: Complications in Patients with Sickle Cell disease (SCD) and Utilization of Iron Chelation Therapy (ICT): A Retrospective Medical Records Review

Description: A retrospective study of sickle cell disease complications.

Methods

In this study data on sickle cell complications, utilization of health care delivery to treat sickle cell complications, transfusion utilization, extent of patients' Transfusional Iron Overload (TIO), and ICT treatment patterns were collected from patient medical charts. Outcomes were compared between transfused patients and non-transfused patients, and, of those patients who have been transfused, between patients who have undergone ICT therapy and those who have not. The study protocol, including the data collection form, was submitted to each Institutional Review Board (IRB) prior to study Initiation.

Objectives

The objectives of the study are to:

(1) Compare transfused vs. non-transfused Sickle Cell Disease (SCD) patients (≥ 16 years) with respect to the following endpoints:

- a. Rates of sickle cell complications (e.g.: pain, infections, stroke)
- b. Utilization of health care delivery to treat the sickle cell complications

(2) Among transfused SCD patients (≥ 16 years), compare those who received ICT vs. those who did not with respect to the following endpoints:

a. Rates of sickle cell complications (e.g.: pain, infections, stroke)

b. Utilization of health care delivery to treat the sickle cell complications

(3) Describe the utilization and reason of blood transfusions over lifetime stratified by key factors (e.g., age)

(4) Describe the extent of iron overload (e.g., through SF readings, total iron binding capacity (TIBC), Liver Iron Concentration(LIC) in patients receiving Iron Chelation Therapy (ICT) over time, including utilization patterns of ICT overall and by age.

Study design: Retrospective cohort study.

Data were collected from patient medical charts. 254 SCD patients \geq 16 years of age from the SCD centers were reviewed. The entire sample was divided into three cohorts based on units of blood transfused over lifetime and whether or not patients received ICT

1) patients receiving < 15 units of blood transfused (Cohort 1, n=69),

2) patients receiving \geq 15 units of blood transfused without ICT (Cohort 2, n=91), and

3) patients receiving \geq 15 units of blood transfused and ICT (Cohort 3, n=94).

Patient flow diagram



Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006 EMA/CHMP/763315/2016

Study population /Sample size:

The medical charts of 254 SCD patients \geq 16 years of age from the SCD centers were reviewed. Of these 254 patients, 117 were from the University of Tennessee, 72 were from Tulane University, and 65 were from Howard University. The patient observation period was at least of 6 months.



Treatments: Among the 254 included patients, 94 transfused patients (cohort 3) received an iron chelating agent: deferoxamine or deferasirox. <u>Only 78 patients received deferasirox</u>.

Outcomes/endpoints

- Sickle cell complications (not complications associated with treatment of SCD or iron chelation therapy)
- Utilization of health care delivery to treat sickle cell complications
- Utilization of blood transfusions (patients with frequent transfusions only)
- Burden of transfusional iron overload (patients with frequent transfusions only)
- Utilization of iron chelation therapy: defined as a prescription of oral suspension deferasirox or administration of subcutaneous deferoxamine. Data of interest included: type of chelator received, frequency, dosage duration : but "The specified scope of this study was not designed to evaluate a specific safety concern or question as in the case for post-marketing surveillance studies or patient registries. However, it was recognized that relevant and important safety information related to a Novartis drug might be discovered in the course of performing a retrospective review of medical records."

Statistical Methods

For each of the endpoints, continuous variables were summarized by mean, standard deviation, median, minimum, maximum (25% and 75% quartiles, as appropriate) and number of patients with non-missing data. Categorical variables were summarized by absolute frequencies and percentages. Unadjusted comparisons of results between cohorts were based on the Pearson χ^2 test for categorical variables and two-sided Student's t-test for continuous variables. An alpha level of 0.05 was used to declare statistical significance. All data manipulations and statistical analyses were performed using SAS version 9.2 software or more recent.

For iron chelators: treatment patterns were assessed using the following measures:

o total number of transfusions/units received at ICT initiation

o SF and other laboratory test levels at ICT initiation

o frequency, dosage, and duration ICT treatment

o switching patterns of ICT treatment (deferasirox to deferoxamine and vice versa)

o ICT treatment interruption and discontinuation

Results

254 patients were reviewed for this study. Across cohorts, the average was 6.6 years for Cohort 1, 8.2 years for Cohort 2, and 8.1 years for Cohort 3. The median age at study index date was 22 years.

In Cohort 3, 99% of patients had at least one SF reading. The mean (sd) number of SF readings per patient was 12 (18) readings. Mean (sd) SF level throughout the observation period was 3,268 (2,902) ng/mL (range: 26-28,124 ng/mL). Liver iron concentration, considered the gold standard for measuring total body iron, was collected for 18 patients, 17 of whom were in Cohort 3. Each patient had one LIC reading, with a mean (median) of 28 (median) mg FE/g dry weight (range of 0-52 mg FE/g dry weight).

Of the 94 patients in Cohort 3, 90 patients received ICT during the observation period, and four patients who received ICT only in the pre-index date (history) period. During the observation period, <u>78 patients received deferasirox</u>, and 29 patients received deferoxamine. Mean (sd) treatment duration was 180 (176) days, and the mean gap between ICT prescriptions was 86 days<u>. Five patients switched from deferoxamine to deferoxamine, and 12 patients switched from deferoxamine to deferasirox. Thirty patients interrupted deferosirox treatment, and seven interrupted deferoxamine. The length of treatment interruption was on average 231 days for the 7 observed deferasirox patients, and 31 days for the two observed deferoxamine patients. Treatment discontinuation was observed for 18 deferasirox patients and six deferoxamine patients. At the time of ICT treatment initiation, patients had a SF reading within 60 days prior to ICT initiation. Among these patients, mean (sd) SF level was 4,985 ng/mL (2,922), a level at least four times above the recommended guidelines for commencing ICT treatment.</u>

This long-term observational study examining real-world treatment patterns, SCD-related complications and associated resource utilization of 254 adults (\geq 16 years old) patients with SCD from three tertiary centers revealed that adult patients with SCD suffered from a significant clinical burden, experiencing on average 1.66 SCD-related complications PPPY among those less frequently transfused patients (Cohort 1) and 2.64 SCD-related complications among those frequently transfused (Cohorts 2 and 3). In this latter group of patients, those receiving chelation therapy were less likely to experience complications than those who didn't.

	Cohort 3 only
	n = 90
Number of Patients Who Switched ICT Treatment	
From Deferasirox to Deferoxamine	5
From Deferoxamine to Deferasirox	12
Number of Patients Who Interrupted ICT Treatment	
Deferasirox	30
Deferoxamine	7
Number of Patients Who Discontinued ICT Treatment	
Deferasirox	18
Deferoxamine	6
Length (Days) of Deferasirox Interruption ($n = 7$)	
Mean \pm SD	231 ± 376
Median [range]	81 [0 - 1,061]
Length (Days) of Deferoxamine Interruption $(n = 2)$	
Mean \pm SD	31 ± 21
Median [range]	31 [16 - 45]

Table 16: Changes in Course of ICT Treatment - Observation Period

CHMP's comments:

Only 78/254 patients received deferasirox in this study.

No specific analyses of the efficacy in paediatric patients have been conducted.

No pediatric patients below 16 years were included in this study. No details are presented for the pediatric population (16 to 18) or on adverse effects reported among patients treated with iron chelators in cohort 3.

This study was not designed to evaluate a safety concern.

2.3.2.3. Study number CICL670ABR01: *RE-LA-T-H Study: A Retrospective Epidemiological Study Of Latin American Patients With Transfusional Hemosiderosis.*

Description: This was an international, multicenter, cross-sectional, retrospective epidemiological study of patients with iron overload secondary to transfusion therapy for chronic anemias. Patients were accrued by tertiary care hematology centers that performed at least 200 monthly consultations, and/or located in cities with at least 1 million inhabitants. A total of 42 sites participated in this study.

Methods:

Objectives:

1. The primary objective of this retrospective epidemiological study was to investigate the magnitude of the problem and patterns of care of iron overload in Latin America, by quantifying the number of patients with transfusion-related iron overload in tertiary-care
hematology centers from Argentina, Brazil, Colombia, Costa Rica, Mexico, Panama, Peru, Trinidad & Tobago, and Venezuela.

- 2. The secondary objectives were :
 - a. to evaluate the severity of iron overload due to transfusion therapy in this world region;
 - b. to analyze the frequency of iron chelation therapy and regimens employed;
 - c. to analyze available compliance therapy with iron-chelating therapy across different countries of Latin America;
 - d. to create a regional knowledge base about iron overload, correlating the main findings with patients' country of origin, ethnicity, diagnosis, and local patterns of care;
 - e. and to evaluate the frequency of clinical consequences of iron overload (cardiac disease, diabetes, growth failure, etc.).

Study design: As a retrospective epidemiological study, it did not test a scientific hypothesis based upon a specific endpoint, and treatment and patient evaluation were left to the discretion of the treating physicians and local standards of care, which were not influenced by this study.

Treatment: There was no investigational drug/reference therapy. No duration of treatment available.

Study period: First patient enrolled: 18-Sep-2006, Last patient completed: 31-Jan-2008.

Study population: 60/975 patients received Exjade.

Statistical methods: All data entered into the system by participating investigators or their designees generated a database containing all information collected from each patient. Such data were summarized by means of tables. Data were analyzed to define the prevalence and clinical features as well as to identify and characterize treatment patterns in four subgroups defined by the primary diagnosis: sickle-cell anemia, thalassemia, myelodysplastic syndrome and other. Descriptive statistics were calculated to summarize population characteristics by subgroup and global. Categorical variables from these patients were compared by means of the chi square test. Continuous variables were compared by Student's t tests. Mean values were reported with +/- 1 standard deviation. Median and interquartile range were also reported when appropriate. Alpha was set at 0.05 and all tests of significance were two-tailed. All statistical analyses were done using SAS® software version 9.1.3.

No safety assessment was performed for this study.

Results:

Recruitment/ Number analysed

Upon study completion, 975 patients were included, 15 of which were excluded from analysis, thus leaving 960 patients. Four hundred and sixty-four patients had sickle-cell anemia (48.3%), 230 had thalassemia (24.0%), 69 had myelodysplastic syndrome (MDS; 7.2%), and 197 had other diagnoses (20.5%).

Baseline data

Demographic characteristics: for sickle-cell disease and thalassemia subgroups, the median age was 21 years.

Iron-chelation therapy: 442 (46.3%) patients received iron-chelation therapy and amongst them 60 patients (13.6%) received deferasirox.

Efficacy results

The study did not report any efficacy information.

Safety results

Complications of iron-chelating therapy were presented for all treated patients (442) without distinction between deferoxamine and deferasirox: No adverse effects were reported in 295 patients (66.7%). Pain/reaction at infusion site were recorded in 83 cases (18.8%) probably related to deferoxamine infusion, allergic reaction in 26 cases (5.9%), gastrointestinal symptoms in 18 cases (4.1%), arthropathy in 2 cases (0.5%), neutropenia/agranulocytosis in 2 cases, liver dysfunction in 3 cases (0.7%), visual abnormalities (unspecified) in 5 cases (1.1%), auditory dysfunction in 3 cases (0.7%), bone abnormalities in 4 cases (0.9%), growth impairment 1 case (0.2%), dermatologic (unspecified) in 5 cases (1.1%), other (unspecified) in 22 cases (5.0%).

Among the main reason for discontinuation of the iron chelation therapy, treatment-toxicity was reported in 6 cases (1.4%).

CHMP's comments:

Only 60/975 patients received Exjade in this study.

This study did not report any efficacy information. Also, this epidemiological study was not designed to evaluate safety data. Complications of iron-chelating therapy were presented for all patients, regardless of the age and the iron chelator, deferoxamine or deferasirox. So no pediatric safety data were available in this study.

2.3.2.2.4. Study number CILC670ADE-04: *Exjade: Post-Marketing Surveillance Study on Tolerability and Efficiency of Exjade® (Deferasirox) in Patients with Transfusion dependent Iron Overload and with Prior Chelation Therapy*

Description: This post-marketing surveillance study entitled 'Exjange' examined the safety and efficacy of the once-daily oral iron chelator Exjade® for the management of chronic iron overload caused by blood transfusions in 109 pre-treated patients.

Methods:

Objectives: to collect data on the safety and efficacy profile of the treatment with Exjade® under daily life treatment conditions in patients suffering from transfusion- dependent iron overload and pre-treated with other iron chelators.

Study design: Post-marketing surveillance study (PMS): a prospective uncontrolled open-labelled, multi center observational study.

Study Population / sample size: The study was conducted among 37 physicians based in pediatric and haematologic-oncologic institutions in Germany. The planned observation period for each subject was 12 months including an initial visit at start of observation period and follow-up visits after about 2, 4, 6, 8, 10 and 12 months.

Study period: from October 2006 to January 2009

Treatment: Exjade®

Outcomes/ Endpoints: During the observation period safety (adverse events and adverse drug reactions) and efficacy data (serum ferritin level) was being collected as generated by usual clinical practice.

Statistical methods: All patients who took at least one dose of Exjade® and had any follow-up information after initial visit were regarded as valid for Intention-to-treat (ITT) analysis.

Descriptive analyses of the data were performed using summary statistics for categorical and quantitative data. Continuous data were described by mean, standard deviation (SD), minimum, 1, 5, 25, 75, 95, 99 percent quantiles, median, maximum, number of non-missing values. In addition, continuous data were categorized in clinically meaningful way. Categorical data including categories of continuous data were presented in frequency tables.

Number of patients with missing data was presented as a separate category. Percentages were calculated as a proportion of each category including the category missing values. In some subgroup analyses percentages were calculated based on non-missing values (adjusted frequencies).

A stratifying analysis was performed for the underlying primary disease (MDS, beta thalassemia and other). Incidence rates for specific adverse events were calculated as the number of specific events reported divided by the number of patients at risk, where the number of specific events was defined as the number of patients reporting the specific event and the number at risk was defined as all patients with consumption of Exjade® during the observation period. For multiple occurrences of a specific event within one patient, the event was counted only once.

Results:

Recruitment/Number analysed: A total of 110 patients participated in this observational study. The first patient entered the study on 1 October 2006, last patient last visit was on 26 January 2009. Out of 110 patients enrolled, 109 were included in the ITT analysis. One patient was lost to follow-up.

Baseline data: A total of 57 male and 52 female patients with iron overload and prior chelation therapy were included in the ITT analysis. Patients' ages ranged from 3 years to 88 years with a median of 62 years.

44 were assigned to the MDS group (40.4%), 33 to the beta thalassemia group (30.3%) and 32 to the group with 'other' primary disease (29.4%). Among 37 patients with specification of another primary disease, "benign, malignant or unspecified neoplasms" was the by far most frequently mentioned MedDRA SOC level (n=24). The most frequently reported other primary diseases by MedDRA Preferred Term were: myelofibrosis (n=6), myeloproliferative disorder (n=4), acute myeloid leukaemia (n=4) and congenital aplastic anemia (n=4).

Population was divided into four age groups : < 16 years, 16 to < 50 years, 50 to < 65 years, and > 65 years. The patients < 16 years represented 7.3% of the total population but 15.2% of betathalassemia and 9.4% for other primary diseases.

Patients with MDS had the highest median transfusional iron intake (0.29 mg/kg/d) with a baseline serum ferritin level to 2442 μ g/L, while those with other primary disease had the lowest (0.15 mg/kg/d) and a baseline serum ferritin to 2635 μ g/L. For patients with beta thalassemia the lowest median baseline serum ferritin level was observed (1864 μ g/L).

All patients had already been exposed to a prior iron chelation therapy: deferoxamine (n=99, 90.8%), deferiprone 28.4% and unspecified "other treatment" (1.8%). For 2 patients the type of prior treatment was unknown. In the beta thalassemia group prior treatment had started earlier compared to the other disease groups (Desferal / Ferriprox start in median years before: MDS: 2.0 / 1.3; beta thalassemia: 7.7 / 3.7; other: 1.6 / 2.0). MDS patients had received lower median daily doses of Desferal when compared to the other disease groups (median daily dosage: MDS: 16.8 mg/kg; beta thalassemia: 40.0 mg/kg; other: 35.0 mg/kg).

The majority of all patients was prescribed an initial dose of 20 - < 30 mg/kg Exjade (n=58, 53.2%). An initial dose of 10 - < 20 mg/kg was prescribed to 30 patients (27.5%). A dose of < 10 mg/kg or \ge 30 mg/kg was administered to 11 and 10 patients (10.1% and 9.2%), respectively. With respect to results of stratified analysis, an initial dose of < 10 mg/kg was more frequently chosen for patients with other primary diseases, whereas beta thalassemia patients more frequently received doses of 20 - < 30 mg/kg. After about 2 months of treatment, for 25.0% (n=26) of all patients was stated that it was necessary to adjust the Exjade® dosage. The following reasons were provided: other reasons (n=10), chelation to poor (n=9), occurrence of an adverse event (n=4), reason missing (n=2) and chelation too strong (n=1). For more than one quarter of patients (n=29, 26.6%) the Exjade® treatment was stopped at any time during the observation period. Reasons for discontinuation of therapy were (multiple responses possible): Occurrence of an adverse event (n=16, 14.7% of all patients), other reasons (n=11) and poor compliance (n=3).

Efficacy results

No specific analyses of the efficacy in paediatric patients have been conducted.

A decrease in SF of 276 ng/ml was reported after 12 months, according to the MAH.

Safety results

<u>Change in serum creatinine and creatinine clearance:</u> For serum creatinine a median increase of 0.1 mg/dl during the study period was observed in 85 patients. The changes in creatinine differed across primary disease subgroups: whereas MDS patients experienced a median increase of 0.2 mg/dl until final visit, beta thalassemia and other disease patients did not show any change in median of differences. For creatinine clearance, a median decrease of 24 mL/min was observed, but this parameter was calculated for only 12 patients.

In summary, 174 adverse events (AE) were documented in 62 out of the 109 patients exposed (56.9%). For a total of 16 patients (14.7%) it was assessed that their events were not serious and there was no causality or only an unlikely causality to Exjade®. An adverse drug reaction (ADR) was documented in respect of 42 patients (38.5%), i.e. the causality to Exjade® was classified as certain, probable or possible or the causality was not assessable. For 20 patients (18.3%) at least one event fulfilled the criteria for a serious adverse event (SAE). For three patients (2.8%) a serious adverse drug reaction (SADR) was reported.

The majority of events occurred in the System Organ Class "Gastrointestinal disorders" (n=39), followed by the Organ Classes "Investigations" (n=33) and "Infections and infestations" (n=18).

On the Preferred Term level, the most commonly reported events were gastrointestinal symptoms like diarrhoea (n=12) and nausea (n=11) as well as blood creatinine increased (n=8). The outcome of the majority of events classified as ADR was assessed as resolved. Six patients died during the study. In none of these six cases a causal relationship to Exjade was supposed.

Adverse events based on all events (n=162) MedDRA – Primary SOC		AE	A	DR	\$	SAE	SADR		Total	
Medbror - Finnary 000	n	%	n	%	n	%	n	%	n	%
Gastrointestinal disorders	4	14.3	32	49.2	3	4.8	0	0.0	39	24.1
Investigations	3	10.7	16	24.6	9	14.5	2	50.0	30	18.5
Infections and infestations*	7	30.4	1	1.5	9	14.5	0	0.0	18	11.1
General disorders and administration site conditions	4	14.3	3	4.6	6	9.7	0	0.0	13	8.0
Respiratory, thoracic and mediastinal disorders	2	7.1	0	0.0	7	11.3	0	0.0	9	5.6
Blood and lymphatic system disorders	3	10.7	0	0.0	5	8.1	0	0.0	8	4.9
Neoplasms benign, malignant and unspecified	0	0.0	0	0.0	7	11.3	0	0.0	7	4.3
Nervous system disorders	2	7.1	4	6.2	1	1.6	0	0.0	7	4.3
Skin and subcutaneous tissue disorders	0	0.0	6	9.2	0	0.0	0	0.0	6	3.7
Injury, poisoning and procedural complications*	1	3.6	0	0.0	4	6.5	0	0.0	6	3.7
Renal and urinary disorders	0	0.0	1	1.5	2	3.2	1	25.0	4	2.5
Muskuloskeletal and connective tissue disorders*	2	7.1	0	0.0	0	0.0	0	0.0	3	1.9
Metabolism and nutrition disorders	0	0.0	0	0.0	2	3.2	1	25.0	3	1.9
Hepatobiliary disorders	0	0.0	0	0.0	3	4.8	0	0.0	3	1.9
Vascular disorders	0	0.0	0	0.0	2	3.2	0	0.0	2	1.2
Ear and labyrinth disorders	0	0.0	1	1.5	1	1.6	0	0.0	2	1.2
Surgical and medical procedures	0	0.0	0	0.0	1	1.6	0	0.0	1	0.6
Eye disorders	0	0.0	1	1.5	0	0.0	0	0.0	1	0.6
Total	28	100.0	65	100.0	62	100.0	4	100.0	162**	100.0

Table 8-17: Adverse Events by MedDRA Primary SOCs and type of events

The three serious ADR were reported in adults: one case of diabetes mellitus (F, 44 y.o) and two cases of renal insufficiency (M, 74 y.o and M, 73 y.o) leading to Exjade discontinuation.

CHMP's comments:

Only 8 children were included in this post-marketing study.

The mean reduction SF is provided for the overall population (ie pediatric and adult). No specific analyses of the efficacy in paediatric patients have been conducted.

Pediatric safety data are not presented separately by the MAH.

Research in the line listing of cumulative report of safety data by system organ class identified only 3 pediatric adverse events (researched by the birth date for an inclusion between 2006 and 2009):

- Increase of transaminases was reported in one child,

- An adolescent has developed a generalized rash,

- Splenomegaly and hepatomegaly with liver disorders and treatment noncompliance with elevation of ferritin, and thrombosis were reported in an adolescent .

2.3.2.2.5. Study number CICL670ADE-05: *Extend: Post-Marketing Surveillance Study on Tolerability and Efficiency of Exjade® (Deferasirox) in Patients with first Treatment of Transfusion-dependent Iron Overload*

Description: a post-marketing surveillance study (PMS), i.e. a prospective uncontrolled open-labelled, multicenter observational study

Methods:

Objectives: The objective of this PMS study was to collect data on the safety and efficacy profile of the treatment with Exjade® under daily life treatment conditions in patients suffering from transfusion- dependent iron overload. The EXTEND study was focused on <u>patients treated the first time</u> with iron chelators.

Study design: The observation period was up to 12 months after start of therapy with follow-up visits after about 2, 4, 6, 8, 10 and 12 months. The study documentation given to each physician consisted of a documentation folder comprising a declaration of consent to participate in the PMS study, an observation plan, the Summary of Product Characteristics as well as five numbered case record forms. The responsible sales reps collected sequentially the completed CRFs from the physicians and passed these onto the CRO. After receipt the pages were registered, the documentation was checked for adverse events and the data were entered in the study database. In the event that the data was incomplete or inconsistent with respect to non-documented or hidden adverse events, queries were sent to the physician requesting completion, checking and/or correction of the data in question. 76 physicians participated.

Study population/Sample size: It was planned to collect valid documentations of up to 300 patients.

Study period: 1 October 2006-29 January 2009

Treatments: Exjade @ was observed within the approved indication within regular practice of the attending physicians. No intervention in the therapeutic decisions of the investigator was allowed. Exjade @ was prescribed in the usual manner in accordance with the terms of the marketing authorization. No additional diagnostic or monitoring procedures were to be applied to the patients.

Outcomes/Endpoints: Every adverse event was to be documented in the CRF, irrespective of whether or not a causal relationship was established between it and Exjade® therapy. The physician was to specify the start and duration of the event, then evaluate the intensity and the causal relationship and document the outcome and any actions that were taken. A basic distinction was to be made between serious and non-serious adverse events.

Statistical methods: All patients who took at least one dose of Exjade® and had any follow-up information after initial visit were regarded as valid for Intention-to-treat (ITT) analysis. Descriptive analyses of the data were performed using summary statistics for categorical and quantitative data. Continuous data were described by mean, standard deviation (SD), minimum, 1, 5, 25, 75, 95, 99 percent quantiles, median, maximum, number of non-missing values. In addition, continuous data were categorized in clinically meaningful way.

Categorical data including categories of continuous data were presented in frequency tables.

Number of patients with missing data were presented as a separate category. Percentages were calculated as a proportion of each category including the category missing values. In some subgroup analyses percentages were calculated based on non-missing values (adjusted frequencies). A stratifying analysis was performed for the underlying primary disease (MDS and other). Incidence rates

for specific adverse events were calculated as the number of specific events reported divided by the number of patients at risk, where the number of specific events was defined as the number of patients reporting the specific event and the number at risk was defined as all patients with consumption of Exjade® during the observation period. For multiple occurrences of a specific event within one patient, the event was counted only once.

Results:

<u>Recruitment/Number analysed:</u> A total of 230 patients participated in this observational study. The first patient entered the study on 1 October 2006 last patient last visit was on 29 January 2009. Out of 230 patients enrolled, 226 were included in the ITT analysis. Patient nos. 1801, 4501, 7301 and 9603 were excluded since only documentation of the first visit of the corresponding CRF was available (lost to follow-up).

Baseline data: Of the 226 patients included in analysis, 123 were assigned to the MDS group (54.4%) and 103 to the group with 'other' primary diseases (45.6%). Ten patients with double response in primary disease variable (MDS and other primary disease) were counted among the MDS group. The most frequently reported "other primary diseases" by MedDRA Preferred Term were: myelofibrosis (n=26), myeloproliferative disorder (n=11), acute myeloid leukaemia (n=11) and aplastic anaemia (n=10). From beta thalassemia and sickle cell anaemia suffered five and four patients, respectively. A total of 118 male and 106 female patients with iron overload and without pre-treatment were included in the ITT analysis (2 patients with missing sex). Patients' ages ranged from 3 years to 91 years with a median of 69 years. No child under 16 years is recognized among MDS patients and 3 children < 16 years (2 children < 6 years and 1 child between 6 and 12 years) with other primary disease were included. The most frequently reported concomitant diseases by MedDRA Preferred Term were: hypertension (n=58), unspecified diabetes mellitus (n=29), type 2 diabetes mellitus (n=20), coronary artery disease (n=17) and hyperuricaemia (n=12). Concomitant treatment was used by 60.6% of all patients. In accordance with the documentation of concomitant diseases, antihypertensive and antidiabetic medications were taken most frequently. Most often an initial dose of 20 - < 30 mg/kg Exjade® was prescribed (n=109, 48.4%). An initial dose of 10 - < 20 mg/kg was prescribed to 59 patients (26.2%). A dose of < 10 mg/kg or \geq 30 mg/kg was administered to 44 and 6 patients (19.6%) and 2.7%), respectively. With respect to results of stratified analysis in initial dosage, no differences between primary disease groups were observed. After about 2 months of treatment, for 19.8% (n=44) of all patients was stated that it was necessary to adjust the Exjade® dosage. The following reasons were provided: chelation too poor (n=16), other reasons (n=14), occurrence of an adverse event (n=11) and reason missing (n=4). In the follow-up visits after about 4 months until final visit the rate of patients with need for dose adjustment was lower and ranged between 10% and 15%. Nine patients discontinued Exjade for adverse event.

Efficacy results

No specific analyses of the efficacy in paediatric patients have been conducted.

A decreased in SF of 723 ng/ml was reported after 12 months, according to the MAH.

Safety results:

<u>Change in serum creatine and creatine clearance:</u> For serum creatinine a median increase of 0.1 mg/dl during the study period was observed. The parameter creatinine clearance was taken only for a small percentage of patients. In 13 patients with pre and post measurement no change was observed.

<u>Hearing test:</u> At initial and last visit, for 27 and 8 patients, respectively, the findings of a hearing test were documented. For none of the 7 patients with pre and post assessment a change was reported.

<u>Ophthalmological examination</u>: The results of an ophthalmological examination were available for 23 patients at initial visit and for 5 patients at final visit. For 4 out of 5 patients with pre and post findings no change was documented, in one patient the pathological finding (mild cataract) of the initial visit was converted to a normal finding according to the age of the patient at the last visit.

<u>Adverse events:</u> 384 adverse events (AE) were documented in 133 out of the 226 patients exposed (58.8%). An adverse drug reaction (ADR) was documented in 73 patients (32.3%), i.e. the causality to Exjade® was classified as certain, probable or possible or the causality was not assessable. For six adult patients (2.7%) a serious adverse drug reaction (SADR) was reported: cataract (1), neutropenia (1), myocardial infarction (1), gastrointestinal hemorrhage (1), blindness (1) renal failure (1). For ADR, the main system organ classes were: Gastrointestinal disorders, General disorders and administration site conditions, Investigations, Skin and subcutaneous tissue disorders. For the serious adverse effects, the involved system organ classes were gastrointestinal disorders, Investigations, Blood and lymphatic system disorders, cardiac disorders, Eyes disorders and renal and urinary disorders. 33 patients died during the observation period (age 57 to 86 years). For the majority of patients the cause of death was related to worsening of their underlying primary diseases.

CHMP's comments:

The mean reduction SF is provided for the overall population (ie pediatric and adult). No specific analyses of the efficacy in paediatric patients have been conducted.

As the pediatric data were not presented separately, the research in the line listing with the birth date provided the following adverse events into children: treatment interruption due to lack of compliance and allogenic bone marrow transplantation in one paediatric patient , ALT and AST increases in another young child . No information about the last child was retrieved.

This PMS study included only 3 children under 16 years of the 226 analyzed patients, which does not describe the pediatric safety profile.

2.3.2.2.6. Study number CICL670AGR01: A non-intervENtional obsERvational study assessing safetY of deferasirox in patients with transfusional iron overload: the 'ENERGY' study

Description: A prospective uncontrolled open-labelled, multicenter observational was performed in Greece during a 12-month. 33% of the sites (6/18) were located in Attica while the rest 67% (12/18) outside Attica. The period of patient recruitment ranged from 14-July-2009 (first patient in) to 23-Dec-2011 (last patient in).

<u>Methods</u>: Safety assessments consisted of monitoring of all adverse events, monitoring and recording of all serious adverse events, regular monitoring of hematology and blood chemistry, as well as regular monitoring of growth and sexual development (weight, height, pubertal stage), ocular and auditory conditions, in accordance with the approved package insert. Also, the following assessment of iron

overload or cardiac function were captured: serum ferritin levels during the study and change from baseline, liver MRI T2*, cardiac MRI T2/T2*, LVEF, LIC. Liver MRI, cardiac MRI, LIC and LVEF were performed at the discretion of the physician during the study.

Objective(s) The primary objective of the study was to assess the safety of deferasirox in patients with chronic iron overload related to blood transfusions applied for the treatment of anemias. Safety assessments consisted of monitoring of all adverse events, monitoring and recording of all serious adverse events, regular monitoring of hematology and blood chemistry, as well as regular monitoring of growth and sexual development (weight, height, pubertal stage), ocular and auditory conditions, in accordance with the approved package insert.

Study design: This was a single-arm, open-label, prospective, non-interventional observational study with the participation of 20 hospital sites (18 hospital sites actually participated) located throughout Greece. The study, provided safety data collected during a 12-month period of treatment with deferasirox. Since this was an observational study, it did not impose a therapy protocol, diagnostic/therapeutic interventions or a strict visit schedule.

Data collection was performed in daily clinical practice and in accordance with the monitoring recommendations for deferasirox as follows:

adverse events

• serum glutamic oxaloacetic transaminase (SGOT) also known as aspartate aminotransferase (AST), serum glutamic pyruvic transaminase (SGPT), also known as alanine aminotransferase (ALT), creatinine, creatinine clearance, proteinuria, cystatin-C (if performed)

- renal histology (if clinically indicated)
- audiological and ophthalmologic assessments
- developmental test (only for children)

Data on concomitant medications were only collected in case of hepatic or renal AEs.

The observance of the following rules has ensured the non-interventional character of this project:

Deferasirox was administered according to the currently approved labeling (SPC).

The investigators' decision-making to administer deferasirox to a patient was based on current medical practice and preceded the consideration of patient's eligibility for enrolment into the study.

The participating patients did not undergo diagnostic or follow-up procedures other than those usually implemented by their treating physician.

□Physicians were only asked to collect and report AEs/SAEs during all visits. Regarding other assessments, physicians were encouraged to complete them only if their use constituted a part of their routine examination practice.

□Statistical analysis of collected data was performed with the use of appropriate descriptive statistical methods.

The study was designed to follow up patients for 12 months. This time period was considered adequate to allow the manifestation and the documentation of the safety profile of study medication.

Study population /Sample size

A total of 230 subjects were enrolled in the study. Of those 4 subjects were assessed as protocol violators. 179 (79.2%) patients completed the 12-month study follow-up, while 47 discontinued prematurely.



Figure 8-2 Diagram of subject enrollment and completion of the study

The study population has been divided in two groups according to the participant's age at the baseline visit. Groups have been defined as: 24 Pediatric patients (Age < 16 years) and 202 Adult patients (Age \ge 16 years).

Thus, the population included in the final statistical analysis comprised of 226 subjects 202 of whom were adults $(38.3\pm10.9 \text{ years})$ and 24 children $(8.7\pm4.2 \text{ years})$. The mean age of the study participants was 35.1 ± 13.8 years with a slight preponderance of females over males (58.0%/42.0%). The pediatric population had a mean age of 8.7 ± 4.2 years and a mean height of 131.3 ± 22.5 cm. The adult population had a mean age of 38.3 ± 10.9 years and a mean BMI of 23.5 ± 3.2 kg/m². Beta-thalassemia major was the most frequently reported (66.8%) reason for transfusion therapy among the overall study population, followed by thalassemia intermedia (17.7%) and sickle cell anemia (9.3%).

Treatment

The majority of the participants (64.2%) were initiated on a dose ranging between 20 and <30 mg/kg/day.

Outcomes/endpoints

During the 12-month follow-up, 34.1% of the overall population did not undergo any dose modifications of their deferasirox treatment, while the remaining 65.9% underwent at least one dose modification. Among those requiring a dose modification, 35.6% (53/149) underwent 1 modification, 25.5% (38/149) underwent two modifications, while the remaining 38.9% (58/149) underwent 3 or more modifications. Treatment was permanently discontinued for 30.2% (45/149), while treatment was temporarily discontinued for 23.5% (35/149). In addition, the dose was only increased in 24.2% (36/149) of the participants, and it was only decreased in 7.4% (11/149).

	Study population	N	Mean	SD	Median	Min	Max
	Overall FAS population	226	1.7	2.0	1.0	0.0	9.0
Number of dose modifications*	Age < 16 years	24	2.7	2.1	2.0	0.0	7.0
mounications	Age \geq 16 years	202	1.6	1.9	1.0	0.0	9.0

The main study population consisted of the remaining 226 patients (FAS). 179 (79.2%) patients completed the 12-month study follow-up, while 47 discontinued prematurely. The main reason for discontinuation of study participation was due to AE (7.1%) followed by loss to follow-up (4.4%).

Two pregnancies occurred during the study, both of which resulted in study discontinuation.

The median duration of study treatment was 11.1 months (range: 0.03-13.6), while for the 47 subjects who prematurely discontinued the study the median time to discontinuation was 6.7 months (0.03-12.1)

Statistical Methods

Analysis of baseline data and all safety analysis have been performed in the Full Analysis Set population. Efficacy analyses performed within the framework of this study have been based on the subsets of patients from FAS with available data in the study efficacy variables. The non-parametric Wilcoxon signed rank sum test has been applied in order to test the change from baseline visit in continuous variables at several time-points of the study. The McNemar's test has been used in order to evaluate the change in the proportion of patients with pathological/normal levels of laboratory exams between baseline and postbaseline visits

Descriptive data

The pediatric population had a mean age of 8.7 ± 4.2 years and a mean height of 131.3 ± 22.5 cm. All subjects were Caucasian. 24 patients <16 years (10.6%) were enrolled. The pediatric population has been divided in three groups according to the participant's age at the baseline visit :

 $2 \le Age < 6 (n=8)$ $6 \le Age < 12 (n=9)$

12≤ Age < 16 (n=7)

Recruitment/ Number analysed

Among the list of inclusion criteria, there were male or female patients with thalassemia and iron overload aged \geq 6 years. Moreover, patients with iron overload and other anemias, or patients aged 2 to 5 years or patients with beta thalassemia and a minor load of blood transfusions may receive deferasirox if treatment with deferoxamine is contraindicated or inadequate, according to the Summary of Product Characteristics.

Baseline data

The pre-baseline assessment for iron overload diagnosis mean serum ferritin levels was 1488.0 ± 976.0 for the paediatric population. At the baseline visit, the mean serum ferritin levels was 1532.7 ± 1002.6 . Of paediatric population, 13/22 had serum ferritin levels above 1000 ng/ml and 100 % out of 3 with available data had normal cardiac MRI T2* (>20 msec) prior to the baseline visit. In 75 % of the 4

patients with available data there was no pre-baseline evidence of liver iron deposition (liver MRI $T2^* > 6,3$ msec). A minority of paediatric participants (9/24) had received iron chelation therapy prior to the initiation of deferasirox. Among pediatric participants the most common prior chelation therapy was DFP alone received by 44.4% (4/9) participants. The mean length of the time period elapsed between deferasirox treatment initiation and study enrolment was 25.9 days (range: 15.0 to 56.0 days). The majority of the paediatric participants (16/24) were initiated on a dose ranging between 20 and <30 mg/kg/day.

Results

Efficacy results

During the 12-month follow-up, among the pediatric population, all but 2 participants (91.7%) underwent dose modifications. The median number of dose modifications was 2 (range: 0-7).

The median duration of deferasirox treatment for the paediatric population was 11.7 months (range: 0.7-14.1 months). Treatment was permanently discontinued in 36.4% (8/22) of the pediatric participants, for which the median time to treatment discontinuation was 5.1 months (range: 0.7-14.0 months).

The changes in serum ferritin levels regarding the paediatric population did not reach statistical significance at any visit (1446.5 \pm 1044.2 at the 12-month visit, p=0.700). The change in the proportion of children regarding serum ferritin values between the baseline (9/22) and the 12-month visit (6/11) was also not evaluated as statistically significant by the Mc Nemar's test (p=0.317). It is noted that the number of patients contributing data to post-baseline assessments of serum ferritin levels is very small hindering appropriate statistical inference (range 8 to 18).

By contrast, for adult participants, the mean change in serum ferritin levels from baseline reached statistical significance at the 12-month visit (1214.0 ± 1008.3 , p=0.009). In addition, the difference in the proportion of participants between the baseline visit (68/119, 57.1%) and the 12-month visit (51/119, 42.8%) that had serum ferritin levels >1000ng/ml was evaluated as statistically significant according to the Mc Nemar's test (p-value=0.007).

Assessment of liver and cardiac MRI, LVEF and LIC during the study was performed only for a small proportion of the study paediatrics participants (6 patients). The median cardiac MRI T2* was 35.0 msec (range: 31.7-40.0 msec), while the median liver MRI was 3.6 msec (range: 2.5-26.0 msec).

Safety results

Main results

The main results of the study include the safety assessment of deferasirox, consisting of all (N)SAEs as well of physiological levels of laboratory parameters (serum creatinine, creatinine clearance, proteinuria, SGOT, SGPT and cystatin C), recording of body weight, height, sexual development and ocular and auditory conditions.

Assessment of laboratory tests during the study

1 Serum creatinine levels

The mean levels appeared to remain relatively constant throughout the study. However, when the mean change in the serum creatinine levels from baseline values at each visit were evaluated with the Wilcoxon signed rank test, slight, albeit statistical significant, increases were observed from Week 1

onwards (p-values ranging from 0.032 to <0.001). The mean serum creatinine levels remained relatively constant for the pediatric population with the change not reaching statistical significance at any time point during the study

2 Creatinine clearance levels

The mean serum creatinine clearance levels remained relatively constant for the pediatric population. The change did not reach statistical significance at any time point during the study.

For the adult population, the decrease in the mean serum creatinine clearance levels was significant throughout the study (Wilcoxon signed rank sum test; p-values ranging from 0.042 to <0.001)

3 SGOT levels

Significant increases in the mean change were not observed at any time point of the study. A statistically significant decrease from baseline levels was noted at the Month 9 visit (Wilcoxon signed rank sum test; p=0.044). The mean SGOT levels for the pediatric population did not reach statistical significance at any time point during the study.

4 SGPT levels

The mean levels tended toward a decrease from baseline values from Week 3 onwards, with the change being statistically significant after the Month 5 visit (p values ranging from 0.014 to <0.001). Statistically significant increases in the mean change were not observed at any timepoint of the study. No statistically significant changes were noted in the SGPT levels for the pediatric population

5 Serum cystatin C levels

The mean serum cystatin C levels remained relatively constant throughout the study, with statistically significant increases noted at the visits of Months 2 (p=0.026), 4 (p=0.014) and 5 (p=0.016) compared to the baseline values using the Wilcoxon signed rank sum test. It is noted that during the study, only a small proportion of participants had available data for their serum cystatin C levels.

No statistically significant changes were noted in serum cystatin C levels for the pediatric population according to data from 1 to 5 pediatric participants

Pathological laboratory values observed during the study

There were no specific trends in the frequencies of patients with pathological values of any of the laboratory measurements for the overall, pediatric and adult population. Pathological levels of proteinuria were observed in 12.5-36.4% of the pediatric study population during the study visits and in 8.2% to 30.8% of the adults. Notably the highest percentage of adult participants with pathological proteinuria levels was observed at the Week 2 visit, while the lowest frequency was observed at the 12-month visit.



Figure 9-5 Percentage of pediatric participants with pathological values during the study

Figure 9-6 Percentage of adult participants with pathological values during the study



Body weight, sexual development, audiological and ophthalmologic

Among the overall population, body weight was recorded for 67 participants during the study.

The mean change from their baseline measurement was 0.3 ± 3.4 kg.

Among the 15 participants that underwent an ophthalmologic examination during the study no change from baseline was recorded for 93.3% (14/15), while an improvement was noted in 1 adult participant

examinations. In regards to the assessment of sexual development among the pediatric population, no change was noted in 6 of the 8 participants (75.0%), while an improvement was noted in the remaining 2 participants (25.0%). In addition, an increase in height and weight was noted in the pediatric population (p<0.001).

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	Ν	Mean	SD	Median	Min	Max	p-value*	
Weight (last available measurement)	18	34.2	19.4	27.0	16.0	82.0		
Change in weight (Baseline- Last available measurement)	18	2.4	2.3	2.5	-2.0	7.0	<0.001**	
Height (last available measurement)	18	132.1	20.9	133.0	107.0	170.0		
Change in height (Baseline- Last available measurement)	18	2.2	2.3	1.0	0.0	9.0	<0.001**	
Change in sexual development ^a	•	•		Ν	•	%		
	No change		6			75.0		
	Impro	vement		2		2	25.0	
		Total	8			100.0		
Change from previous audiological test				Ν			%	
No change		3			75.0			
Improvement		1			25.0			
Total			4			100.0		
Change from previous ophthalmologic	test			Ν			%	

Table 9-79	Changes in	anthropometric	characteristics	of	pediatric	participants
	during the st	udy				

Adverse events and adverse reactions

The overall AE incidence during the study irrespective of seriousness and causal relationship with deferasirox was 50.0%; in particular the incidence of NSAEs and SAEs was 45.6% and 9.3%, respectively, while the relevant incidence of NSADRs was 28.8% and of SADRs 1.3%. It is worth mentioning that only 13 SAEs were assessed as deferasirox-related. The overall all-cause mortality rate was 0%.

No change

Total

5

5

100.0

100.0

(N)SAE and (N) SADR resulting in study or treatment discontinuation

The number of patients who discontinued the study due to (N)SAE was 16 (7.1%). More specifically, 12 adults (5.3%) and 4 children (1.8%) discontinued the study due to an (N)SAE.

The overall treatment discontinuation rate due to (N)SAE occurrence was 11.5% (26 participants). Of the adult population 9.7% (n=22) terminated deferasirox treatment due to (N)SAE, while the respective percentage for the pediatric population was 2.2% (n=5).

n=226	N _{events}	N _{patients}	%
AEs (Serious and Non-Serious)	412	113	50.0
NSAEs (Non-Serious AEs)	356	103	45.6
NSADRs (Non-serious adverse drug reactions)	167	65	28.8
SAEs (Serious AEs)	56	21	9.3
SADRs (Serious adverse drug reactions)	13	3	1.3

Table 9-80 Incidence of (N)SAEs and (N)SADRs

Analysis of non-serious adverse events (NSAEs)

A total of 356 NSAEs were reported by 103 (45.6%) participants 78.4% (279/356) were mild, 16.6% (59/356) moderate and 5.1% severe (18/356). 317 NSAEs were reported by 88 adult participants with an incidence greater than 3% were (in descending frequency order):

blood creatinine increase (7.4%), respiratory tract infection (6.4%), upper abdominal pain (5.9%), diarrhea (5.4%), and creatinine clearance decrease (3.5%). 39 NSAEs were reported by 15 children (62.5% of the pediatric population). The most common NSAEs in children were blood creatinine increase (16.7%) and increases in transaminases (8.3%) and the urine albumin/creatinine ratio (8.3%), albuminuria (8.3%), hypercalciuria (8.3%), gastroenteritis (8.3%), respiratory tract infection (8.3%) and diarrhea (8.3%)

Analysis of non-serious adverse drug reactions (NSADRs)

A total of 167 of the 356 NSAE were NSADRs and were reported by 65 (28.8%) participants, 65.9% (110/167) were mild, 23.4% (39/167) moderate and 10.8% severe (18/167).

141 NSADRs occurred in 54 adult participants (26.7% of the adult population) with a frequency greater than 3% of the adult population were (in descending frequency order): blood creatinine increase (7.4%), upper abdominal pain (5.4%), diarrhea (4.0%), and creatinine clearance decrease (3.5%)

26 NSADRs were experienced by 11 pediatric participants (45.8% of the pediatric population). The most common NSADRS in the pediatric population were: blood creatinine increase (16.7%), increases in transaminases (8.3%), albuminuria (8.3%), and hypercalciuria (8.3%)

Analysis of SAEs

A total of 56 SAEs were reported by 21 participants (9.3% of the overall study population). Only abdominal pain (1.8%) and pyrexia (1.3%) were reported at a frequency \geq 1%

48 SAEs were reported by 18 adult participants (8.9% of the adult population). The SAEs reported with a frequency $\geq 1\%$ in the adult population, were abdominal pain (1.5%) and pyrexia (1%).

8 SAEs were reported by 3 pediatric participants (12.5% of the pediatric population). These events included one event each of abdominal pain, **rectal prolapse**, hemolysis, pyrexia, gastroenteritis, increase in alanine aminotransferase, increase in blood albumin, and back pain

Analysis of SADRs in the adult population

Ten SADRs were reported in 2 adult participants (1% of the adult population) .Nine of the SADRs (90%) were severe and 1 (10%) was moderate All SADRs had resolved by study completion

Analysis of SADRs in the pediatric population

3 SADRS were reported by a single pediatric participant (4.2% of the pediatric population). They included rectal prolapse, alanine aminotransferase increase and blood albumin increase and were all characterized as severe in terms of their intensity. Furthermore, all 3 events had resolved by the time of study completion

Table 9-102 SADRs by MedDRA SOC and PT, adult population

n=202		
MedDRA SOC	N	
MedDRA PT	Npatients	% 0
Gastrointestinal disorders	2	1.0
Abdominal pain	1	0.5
Abdominal pain upper	1	0.5
Chemical peritonitis	1	0.5
Gastric ulcer	1	0.5
Gastric ulcer perforation	1	0.5
Localized intraabdominal fluid collection	1	0.5
Pelvic fluid collection	1	0.5
Peritoneal disorder	1	0.5
Rectal prolapse	1	0.5
Musculoskeletal and connective tissue disorders	1	0.5
Musculoskeletal pain	1	0.5
Surgical and medical procedures	1	0.5
Cholecystectomy	1	0.5

Table 9-104 SADRs by MedDRA SOC and PT, pediatric population

n=24			
MedDRA SOC	N	0/-	
MedDRA PT	1 patients	% 0	
Gastrointestinal disorders	1	4.2	
Rectal prolapse	1	4.2	
Investigations	1	4.2	
Alanine aminotransferase increased	1	4.2	
Blood albumin increased	1	4.2	

Table 9-105 Distribution of SASRs by intensity and outcome, pediatric population

SADRs by intensity (n=3)	N _{events}	%
Mild	-	-
Moderate	-	-
Severe	3	100.0
Total	3	100.0
SADRs by outcome (n=3)	N _{events}	%
Resolved	3	100.0

Discussion

A total of 226 participants 24 of whom were children (8.7 ± 4.2 years) comprised the study population analyzed, 4 children (1.8%) discontinued the study due to an (N)SAE. Treatment discontinuation due to (N)SAE was noted for 5 (2.2%) children.

A total of 167 of the 356 NSAE were NSADRs (i.e. recorded as related to study medication). The NSADRs were reported by 65 (28.8%) participants. 141 NSADRs occurred in the adult population, while the remaining 26 in the pediatric population.

Furthermore, 56 SAEs were reported by 21 participants (9.3%). The SAEs reported with a frequency \geq 1% in the adult population, were abdominal pain (1.5%) and pyrexia (1%). Of the 48 SAEs reported in the adult population, 39 (81.3%) were severe. A total of 8 SAEs were reported by 3 pediatric participants. The majority of the SAEs reported by the pediatric population were of moderate intensity (62.5%), while the remaining were severe (37.5%). Of the 56 SAEs, 91.1% had resolved by the end of the study.

Of the 56 SAEs, 13 were assessed as related to the study medication (SADRs). Ten SADRs were reported by 2 adult participants, while 3 SADRS by a single participant of the pediatric population.

CHMP's comments:

Twenty-four (24) patients <16 years were enrolled in this observational study. The pediatric population had a mean age of 8.7 ± 4.2 years.

Efficacy data

The interpretation of the presented data is limited, and the results only have an observational value, due to:

- The lack of paediatric results being analyzed separately,

- The design of the study: open-label, non-randomized, non-controlled with main limitations including potential selection bias, missing data and lack of internal validity.

As a reminder, the MAH submitted this clinical study report in the context of article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. A clear description of patient exposure and dose interruption data done by age group in order to compare paediatric and adult population would have been expected.

Regarding these elements no conclusion in terms of efficacy of deferasirox in paediatric population can be drawn. On the contrary, from the data presented above, efficacy in reducing iron overload appears to be lower than in adult population.

Safety data

The safety result is reported by adult and pediatric population but not in sub group $2 \le Age < 6$; $6 \le Age < 12$; $12 \le Age < 16$ (n=7).

Information about the patient who developed rectal prolapse is not available. Furthermore, this AE is not mentioned as an adverse effect in SCP of defensions.

The frequency of **NSDAEs** and **SADRs** seems higher in pediatric population 45.8% and 4.2% respectively rather than in adult population 26.7% and 1% respectively.

2.3.2.7. Study number CICL670AIC02: Assessing Iron Overload in Transfusion-dependent patients by MRI in Latin America (ASIMILA Study)

Description: Evaluation of the use of MRI R2 and T2* techniques to assess iron overload in transfusion-dependent patients in conditions such as sickle cell disease, myelodysplastic syndrome or other chronic anemias.

<u>Methods</u>:

Objectives:

• Primary objectives

1. To determine the prevalence and the extension (severity) of liver and cardiac IOL in transfusiondependent patients with Myelodysplastic Syndromes, Aplastic Anemia, Diamond Blackfan Anemia (DBA), congenital sideroblastic anemia, or other rare anemias using MRI R2 and MRI T2*, respectively;

2. To determine the prevalence and the extension (severity) of liver IOL in transfusion dependent patients with homozygous Sickle Cell Anemia (SCA) using MRI R2.

- Secondary objectives
- 1. To investigate the correlation between liver IOL and serum ferritin (SF) levels;
- 2. To investigate the correlation between myocardial IOL and SF levels;
- 3. To assess the relationship between liver IOL and hepatic complications;

4. To assess the relationship between myocardial IOL and cardiac complications;

5. To assess the relationship between echocardiogram and myocardial IOL;

6. To correlate echocardiography findings and cardiac MRI findings in the subset of elderly MDS patients.

Study design: This is an open, multicenter, observational study of patients with liver or cardiac IOL secondary to transfusion therapy for chronic anemias. This study will not test a scientific hypothesis based upon a specific endpoint. The treatment and patient evaluation will be left to discretion of the treating physicians and local standard of care.



Study population/ Sample size: Patients with a known underlying disease related to transfusional IOL: homozygous Sickle Cell Anemia (SCA), low-risk and intermediate-I Myelodysplastic Syndromes (MDS), Aplastic Anemia (AA), Diamond Blackfan Anemia (DBA), congenital sideroblastic anemia, or other rare anemias. Male and female patients older than 10 years of age were eligible. Lifetime history of > 20 units of RBC transfusions with SF level > 2000 ng / ml OR 20 or more lifetime transfusions regardless of SF level. It was estimated that approximately 200 patients who met inclusion and exclusion criteria would be recruited from tertiary care institutions of Latin America.

A total of 52/212 patients received Exjade, 103 patients in total were treated for iron overload.

Study period: 01-Nov-2011 to 28-Mar-2013

Treatments: this study did not involve study drug and also there were no recommendations or guidelines regarding IOL treatment. Patients should have been treated according to the local standard of care.

Outcome/endpoints: Safety assessment:

For the purposes of this study, the main focus will be on the collection of the following information for medication used to treat IOL:

- 1. reason for dose/regimen change and/or not taking treatment as prescribed and
- 2. reason for death (if any)

The collection of this information was entered in the proper section of the eCRF. No other AE was solicited in this protocol. Adverse events that occurred prior to start ASIMILA protocol were processed as medical history. Each of the following subset of AEs will be summarized:

AEs reported as serious

- AEs with CTCAE grade III or IV
- AEs causing permanent discontinuation of current treatment
- AEs requiring concomitant medication
- AEs requiring hospitalization/prolonged hospitalization
- AEs related to current treatment

Statistical methods: Descriptive statistics for an observational study: Frequency and percentage are used for categorical and ordinal variables Number of non-missing values (n), mean, standard-deviation (SD), median, minimum and maximum values are used for continuous variables.

Recruitment/ Number analysed: A total of 212 subjects were enrolled in the study. Thirty seven subjects were not included in the FAS due to: failure on inclusion or exclusion criteria (6 subjects), failure to perform key procedures – MRI (25), protocol deviation at visit 1 not accepted by Ethics Committee (4) and withdrew consent (2). One-hundred and seventy-five subjects were taking into account for the analysis.

Baseline data: The mean age at study entry was 34.6 ± 17 years, 29 pediatric patients, and female gender was predominant (54.3%). Population was more or less evenly distributed among 3 ethnic groups, Caucasian 31.4%, Hispanic 31.4% and Black / African 29.1%. 103 patients in total were treated for iron overload. 50.3% of treated patients received Exjade, 8.6% deferoxamine and 4.0% used deferiprone.

Results

Efficacy results:

No specific analyses of the efficacy in paediatric patients have been conducted according to the iron chelation therapy.

A high percentage of patients had abnormal liver MRI (76%). In addition, a high severity score for a significant number of patients was observed.

Safety results: Fourteen subjects (8.0%) have at least one adverse event (AE). There is 1 subject with serious AE (0.6%); 2 with grade III AE (1.1%); 1 with AE causing permanent discontinuation of current treatment (0.6%), 4 with AE requiring concomitant medication (2.3%), 1 with AE requiring hospitalization/prolonged hospitalization (0.6%) and 3 with AE related to current treatment

Transaminases increased (1.1%) and iron overload (1.1%) are the most often reported adverse events. A total of 5 patients required drug discontinuation or drug treatment related to any adverse event, as shown below. Four patients required concomitant medication to treat the adverse event, and included bone marrow failure related to progression of underlying disease (1 pt), iron overload related to excess of transfusions to treat underlying disease (2 pts) and thrombosis (1 pt). One patient discontinued drug (unspecified) for AE (unspecified) affected hepatobiliary system.

Adverse events, by primary system organ class and preferred term:

Primary System Organ Class (SOC) and Preferred Term (PT) * - n (%)	
Any primary SOC Total	14 (8.0%)
Investigations Total Transaminases increased Echocardiogram abnormal Haemoglobin decreased	4 (2.3%) 2 (1.1%) 1 (0.6%) 1 (0.6%)
Metabolism and nutrition disorders Iron overload	2 (1.1%)
Blood and lymphatic system disorders Bone marrow failure	1 (0.6%)
Gastrointestinal disorders Diarrhoea	1 (0.6%)
Hepatobiliary disorders Hepatitis	1 (0.6%)
Infections and infestations Urinary tract infection	1 (0.6%)
Injury, poisoning and procedural complications Ligament sprain	1 (0.6%)
Reproductive system and breast disorders Testicular pain	1 (0.6%)
Surgical and medical procedures Tooth extraction	1 (0.6%)
Vascular disorders Thrombosis	1 (0.6%)
Total of subjects	175

CHMP's comments:

Twenty-nine (29) children aged 10 to 18 were included in the study. However, this observational study was not built to assess the efficacy and safety of deferasirox in children. Furthermore, a total of 103/212 patients received an iron chelator therapy, which 50.3 % (52) with deferasirox, but the proportion of treated children is not specified.

This study did not report any efficacy results presented separately according to the iron chelation therapy.

Fourteen (14) adverse events were identified but distribution by age is not available and treatment received by these patients is not specified. Among these 14 adverse events, 3 events were related to treatment but we have no information on age, treatment and drug adverse effect for these patients.

2.3.2.2.8. Study number CICL370AKR01: Regulatory Post-marketing Surveillance Report for Exjade® Tablet

Description: Regulatory Post Marketing Surveillance

<u>Methods</u>: This is an open-label, multicenter, single-arm, observational post-marketing surveillance. This surveillance was conducted for 6 years, from 31 March 2006 to 30 March 2012, and application for New Drug Re-examination was made between 31 March 2012 and 30 June 2012. Each patient was followed up to a maximum of 12 weeks. Study doctors consecutively enrolled all patients who had received at least one dose of the study drug to reach the planned number of patients. The subjects were patients who were treated with the study drug by the study doctor for the approved indications, and enrolled in this study after the clinical decision on the use of the study drug was made.

Each subject could discontinue the study drug at any time, and then the subject's benefits were given the first priority.

Objectives: To identify the problems and questions associated with the followings for Exjade® (deferasirox) under the real-life conditions in its approved indications.

- (1) Unknown adverse reactions (especially serious adverse reactions)
- (2) Incidence of adverse reactions under the routine drug use
- (3) Factors that may affect the safety of the drug
- (4) Factors that may affect the efficacy of the drug

Study design: This is an open-label, multicenter (37 centers), single-arm, observational post-marketing surveillance.

Inclusion criteria:

1. Patients who were decided to be treated with the study drug according to "Indications"

(transfusion-dependent hemosiderosis)

2. Patients who were decided to be treated with the study drug according to the current

authorized "Precaution for use".

Exclusion criteria:

- 1. Known hypersensitivity to the active substance or any of the excipients of the study drug
- 2. Daily doses exceeding 40mg/kg

Study population/ Sample size: Planned subject number: At least 1,200 patients at 100 study centers.

Study period: 16-Nov-2006 to 19- Mar-2012

Treatments: Exjade® (deferasirox) Tablet is a therapeutic drug for hemosiderosis which occurs in transfused patients, and detailed description is included in "Dosage and Administration" of the current labeling. 12 weeks of follow up.

Outcomes/Endpoints: Safety: - Adverse event and Serious adverse event

Statistical methods: Safety analysis:

The assessment of safety was performed as follows based on the frequency of adverse events including serious adverse events.

(1) Summary of incidence of adverse events: All incidences of adverse events were summarized, and serious adverse events and unknown adverse events (which are not included in "Precaution for use") were summarized and presented.

(2) Incidence of adverse events by type: Incidence rate of adverse events was summarized and presented by system organ class based on MedDRA ver 15.1.

(3) Trend of incidence of adverse events by factor

- Incidence of adverse events by patient background factor

Incidence of adverse events was summarized and presented by factors including sex, age, body weight, creatinine level, transfusion (total number/volume of transfusion, total years of transfusion), presence or absence of allergy history, presence or absence of concurrent

disease, actual duration of Exjade use, dose of Exjade, and presence or absence of concomitant medication, and was analyzed using Chi-square test or Fisher's exact test if possible.

- Classification of adverse events

Adverse events were summarized and presented by details including severity, action(s) taken, outcome, and relationship to the study drug.

- Adverse events in special population Incidence of adverse events in special patient population, e.g., geriatric or pediatric patients, pregnant women, patients with renal impairment, patients with hepatic impairment, and patients with prolonged use, was analyzed separately.

(4) Factors that may affect the safety

Logistic regression analysis was performed with factors that may affect the incidence of adverse events, e.g. sex, age, allergy history, transfusion, past medical history, concurrent disease, duration of Exjade® use, dose of Exjade®, presence of absence of concomitant medication, as independent variables and presence or absence of adverse events as a dependent variable, to examine the effect of the above factors on the safety outcome.

Results:

Recruitment/Number analysed: Case report forms (CRFs) of 1,579 subjects were collected, including 209 patients \geq 2 to < 12 years (13.2%). Of the collected 1,579 cases, 1,530 subjects were included in the safety population, excluding 32 subjects who completed study drug administration before contract date, 1 subject who violated inclusion/exclusion criteria, and 16 subjects contraindicated for study drug.

Efficacy results

No specific analyses of the efficacy in paediatric patients have been conducted.

A reduction of 417 ng/ml in mean SF after 12 weeks was observed.

Safety results

A total of 138 serious adverse events (SAEs) were reported in 92 subjects (6.01%) of 1,530 subjects in the safety population during this Re-examination investigation period. Listing the reported SAEs by preferred term in decreasing order of number of cases, 'Pneumonia' was reported in 1.31% (20/1,530 subjects), 'Pyrexia' in 0.72% (11/1,530 subjects), and 'Sepsis' and 'Febrile neutropenia' in 0.52% (8/1,530 subjects) each, etc. Of these events, 'Blood creatinine increased' and 'Otitis media' in 0.07% (1/1,530 subjects) each were serious adverse drug reactions of which the relationship to the study drug could not be ruled out.

A total of 660 unexpected adverse events (AEs), irrespective of relationship to the study drug, were reported in 376 subjects (24.58%) of 1,530 subjects in the safety population during this Reexamination investigation period. Listing the reported unexpected AEs by preferred term in decreasing order of number of cases, 'Febrile neutropenia' was reported in 4.84% (74/1,530 subjects), 'Upper respiratory tract infection' in 2.16% (33/1,530 subjects), 'Decreased appetite' in 1.83% (28/1,530 subjects), and 'Cough' in 1.50% (23/1,530 subjects), etc.

A total of 76 unexpected adverse drug reactions (ADRs) were reported in 72 subjects (4.71%) of 1,530 subjects in the safety population Listing the reported unexpected ADRs by preferred term in decreasing order of number of cases, 'Azotaemia' was reported in 0.59% (9/1,530 subjects), 'Decreased appetite'

in 0.52% (8/1,530 subjects), 'Blood urea increased' in 0.46% (7/1,530 subjects), and 'Hypophagia' in 0.26% (4/1,530 subjects), etc.

A total of 1,449 AEs were reported in 677 subjects (44.25%) of 1,530 subjects in the safety population during this Re-examination investigation period. Listing the reported AEs by preferred term in decreasing order of number of cases, 'Febrile neutropenia' was reported in 4.84% (74/1,530 subjects), 'Alanine aminotransferase increased' in 4.25% (65/1,530 subjects), 'Nausea' in 4.18% (64/1,530 subjects), and 'Aspartate aminotransferase increased' in 3.99% (61/1,530 subjects), etc.

A total of 461 ADRs were reported in 325 subjects (21.24%). Listing the reported ADRs by preferred term in decreasing order of number of cases, 'Blood creatinine increased' was reported in 2.94% (45/1,530 subjects), 'Nausea' in 2.75% (42/1,530 subjects), 'Rash' in 2.61% (40/1,530 subjects), and 'Alanine aminotransferase increased' in 2.55% (39/1,530 subjects).

With severity of AEs classified into 3 categories, 'Mild', 'Moderate', and 'Severe', 69.71% (1,008/1,446 cases) of AEs were 'Mild', 25.24% (365/1,446 cases) 'Moderate', and 5.05% (73/1,446 cases) 'Severe'.

Action taken after occurrence of AE was 'Concomitant medication/Non-drug treatment' in 43.96% (637/1,449 cases), 'None' in 25.26% (366/1,449 cases), 'Permanent discontinuation' in 13.25% (192/1,449 cases), and 'Dose modification/Temporary interruption' in 9.25% (134/1,449 cases), etc.

With outcome of AE classified into 4 categories, 'Resolved', 'Recovering', 'Ongoing', and 'Death', 81.15% (1,171/1,443 cases) were 'Resolved', 9.08% (131/1,443 cases) 'Ongoing', 5.41% (78/1,443 cases) 'Recovering', and 4.37% (63/1,443 cases) 'Death'.

With relationship between AE and the study drug classified into 7 categories, 'Certain', 'Probable/Likely', 'Possible', 'Unlikely', 'Unknown', 'Conditional/Unclassified', and 'Unassessible/Unclassifiable', 68.18% (988/1,449 cases) were 'Unlikely', 24.02% (348/1,449 cases) 'Possible', 4.97% (72/1,449 cases) 'Probable/Likely', and 1.52% (22/1,449 cases) 'Conditional/Unclassified'.

CHMP's comments:

The mean reduction SF is provided for the overall population (ie pediatric and adult). No specific analyses of the efficacy in paediatric patients have been conducted.

209 pediatric patients (13.2% of the recruited patients) were enrolled in this study: this is the largest number of children included. Nevertheless, the report submitted for analysis is only the study's synopsis and pediatric results were not presented separately, while the study planned to present incidence of adverse events by factors including age or adverse events in special population, e.g pediatric patients. The objectives are not achieved.

2.3.2.2.9. Study number CICL670ASE01: Observational study evaluating safety and efficacy of Exjade (deferasirox) in transfusional dependent anemias (EXTRA)

Description: This was an open-label, non-randomized observational study in patients treated with Exjade® for transfusional hemosiderosis to evaluate clinical efficacy and safety.

Methods:

Objectives: The overall objective of the study was to evaluate the safety and efficacy of Exjade® in transfusional dependent anemias. The primary objectives of this study were:

- To evaluate the safety of treatment with Exjade® when used in a naturalistic setting reported as adverse events (AE) and serious adverse events (SAE) and by collecting information on renal and hepatic safety (following serum creatinine and serum transaminases).
- To evaluate the clinical response to treatment with Exjade® (by following serum ferritin)
- To evaluate patient or patient's parent/caregiver reported compliance and satisfaction with Exjade® treatment.

Study design: This was an open-label, non-randomized observational study in patients treated with Exjade® for transfusional hemosiderosis to evaluate clinical efficacy and safety. Assessment of methods and parameters used in daily practice were performed at each planned visit for Exjade® treatment, usually every month. Patients were observed in the study for a maximum of 2 years. The occurrence of any AEs (including SAEs), the patients' consumption of Exjade® (including patient reported compliance) and the use of concomitant medications were noted in the electronic case report forms (eCRFs) by center personnel. Selected laboratory data (including serum ferritin, serum transaminases and serum creatinine) acquired from common daily practice were recorded in the eCRFs after local analysis. Furthermore, the treatment satisfaction in terms of health status was assessed by the use of a Visual Analogue Scale (VAS), if this was part of the common practice at the center.

Study population/ Sample size: The study population consisted of patients with chronic iron overload due to blood transfusions:

- patient aged more than 6 years with beta-thalassemia major with iron overload due to frequent blood transfusions,
- patients with iron overload where treatment with deferoxamine is contraindicated or insufficient in patients :
 - o with other anemias,
 - o age 2-5.
 - o with beta-thalassemia major

Patients without any earlier treatment for their iron overload as well as patients treated with iron chelators were included. The decision to treat the patient with Exjade® had to fall within the current practice at the hospital and had to be clearly separated from the decision to include the patient in the study.

Study period: 29-Aug-2006 to 19-Sep-2012

Treatments: Patients were treated with deferasirox (Exjade®) as prescribed by the investigator under the country specific regulations and in agreement with the Prescribing Information/Package Insert.

Outcomes/Endpoints:

- Safety
 - Serum transaminases and serum creatinine were recorded in the CRF. Other laboratory parameters were also recorded if measured in common clinical practice.

 Tolerability/Safety assessments consisted of monitoring and recording of Adverse events and serious adverse events. Pregnancies were reported and measurements of growth (weight and height in children), ocular test and auditory test were performed annually.

Statistical methods: The data from all centers were pooled and summarized with respect to demographic and baseline characteristics and safety and efficacy observations. Summary statistics was presented in total and by site. Exploratory analyses were performed using descriptive statistics. Data were presented for the complete intent-to-treat (ITT) population. The assessment of safety was based mainly on the frequency of AEs, which included all SAEs. AEs were summarized by presenting the number and percentage of patients having any AE, the number and percentage of patients having an AE specified for the various body systems and the number and percentage of patients having specific AEs. Any other information collected (e.g. severity) was listed as appropriate. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 16.0, and presented by System Organ Class (SOC) and Preferred Term (PT).

Descriptive statistics for continuous variables were summarized as number of observations (n) mean (standard deviation [SD]), median, minimum (Min) and maximum (Max) values. Categorical values were presented using frequency (n) and percentage (%).

Results:

Recruitment/Number analysed: 60 patients were enrolled from 16 centers: one in Denmark and 15 in Sweden. All the patients were treated with deferasirox. Of the enrolled patients, 21 (35.0%) completed the 24 months observation period, 32 (53.3%) discontinued and 7 (11.7%) had missing data. Half of the population (32 patients, 53.3%) discontinued from the study prior to 24 months observation mainly due to adverse events: 18 patients (56.3%) discontinued of adverse events, 12 patients (37.5%) discontinued for other reasons (detail of other reasons: death (6), patient's decision (2), lost of follow up (1), bone marrow transplantation (2), discontinuation of blood transfusions (1)) and 2 patients (6.3%) for inefficacy.

Baseline data: The majority of the study population was males (39 patients [65%]) and the mean age at baseline was 62 years (range: 10 to 93 years). There was 1 patient below the age 18 years at inclusion (aged 10 years). The most common diagnosis was "Other anemia" (28 patients [46.7%]) followed by "MDS" (23 patients [38.3%]) and "Thalassemia" (9 patients [15.0%]). No patient had Sickle-cell anemia (0%). At baseline previous iron chelation therapy had been administered as follows: Exjade® to14 patients, Desferal® to 21 patients and Ferriprox® to 18 patients. Of the 14 patients previously treated with Exjade®, half of them (7 patients) had experienced AEs related to the treatment. Among those that had received previous Exjade® treatment, the mean initial daily dose of Exjade® was 18.8 mg/kg. There were 51 patients (85.0%) with at least one concomitant medication. The most common therapeutic subgroups were "Antianemic Preparations" and "Antibacterials for Systemic Use" in 21 patients (35.0%) respectively followed by "Antineoplastic Agents" in 14 patients (23.3%).

Efficacy results

No specific analyses of the efficacy in paediatric patients have been conducted.

According to the MAH, a decreased from BL in mean SF of 2977ng/ml to 1577 ng/ml after 24 months is noted.

Safety results:

• <u>Serum creatinine</u>: the mean of serum creatinine value varied between 76 (baseline) and 89 µmole/L (month 9).



Mean Serum Creatinine Value over Time

• <u>Creatinine clearance:</u>

Mean Creatinine Clearances over Time



• <u>Serum transaminases:</u> Mean values of serum transaminases over time are presented in figure below. Extreme value(s) at Month 9 resulted in a high mean value of 6.7 (range: 0.22 to 139) which affects the curve, **but the cause of these high mean value was not specified.**



- <u>Hematology parameters:</u> stable over time in general. The median hemoglobin value was always around 90 g/L and varied from 89 (Month 15 and 18) to 92 g/L (Month 3). The median white blood cell count varied from 4.0 x109/L (Month 3) to 5.6 x109/L (Month 21). For neutrophils the median varied from 1.7 x109/L (Month 6) to 2.9 x109/L (Month 15 and 21). The median for platelets was between 290 x109/L (Month 21) and 138 x109/L (Month 3).
- <u>Chemistry:</u> Albuminuria was only reported for a few patients.
- <u>Adverse events:</u> A total of 247 adverse events (AEs) were reported in 49 (81.7%) patients and 22 patients (36.7%) experienced a serious adverse event (SAE). Twelve (12) patients (20.0%) died due to SAEs/AEs. It should be noted that it is unknown if the AEs that resulted in death were reported as SAEs or not. AEs that were "Probably" related to Exjade® were reported for half of the population (50.0%). It was most common on a patient level to have experienced AEs "Unlikely" to be related to Exjade® treatment (56.7%). AEs "Possibly" related to Exjade® were most commonly reported for 35.0% and the relationship was "Not assessable" for 1.7%. AEs were most commonly reported within the following SOCs: Gastrointestinal disorders in 56.7% of the population, General disorders and administration site conditions and Infections and infestations in 28.3% of the population respectively. The most common PT among the SOC Gastrointestinal disorders was "Diarrhoea" in 33.3% of the population, followed by "Abdominal pain" in 14 patients (23.3%) and "Vomiting" in 10 patients (16.7%).

Summary of Number of Adverse Events by System Organ Class

	N=60
System Organ Class	n (%)
Gastrointestinal disorders	34 (56.7%)
General disorders and administration site conditions	17 (28.3%)
Infections and infestations	17 (28.3%)
Investigations	10 (16.7%)
Skin and subcutaneous tissue disorders	10 (16.7%)
Nervous system disorders	9 (15.0%)
Musculoskeletal and connective tissue disorders	7 (11.7%)
Blood and lymphatic system disorders	5 (8.3%)
Metabolism and nutrition disorders	5 (8.3%)
Eye disorders	4 (6.7%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	4 (6.7%)
Respiratory, thoracic and mediastinal disorders	4 (6.7%)
Renal and urinary disorders	3 (5.0%)
Reproductive system and breast disorders	3 (5.0%)
Immune system disorders	2 (3.3%)
Psychiatric disorders	2 (3.3%)
Social circumstances	2 (3.3%)
Vascular disorders	2 (3.3%)
Cardiac disorders	1 (1.7%)
Hepatobiliary disorders	1 (1.7%)
Injury, poisoning and procedural complications	1 (1.7%)
Not yet coded	1 (1.7%)
Surgical and medical procedures	1 (1.7%)

Summary of Specific Adverse Events by Relationship

		R	elationship (N=60))	
System Organ Class	Total	Probable	Possible	Unlikely	Not Assessable
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)
Gastrointestinal disorders	34 (56.7%)	25 (41.7%)	9 (15.0%)	6 (10.0%)	0 (0.0%)
Diarrhoea	20 (33.3%)	17 (28.3%)	2 (3.3%)	2 (3.3%)	0 (0.0%)
Abdominal pain	14 (23.3%)	8 (13.3%)	6 (10.0%)	3 (5.0%)	0 (0.0%)
Vomiting	10 (16.7%)	5 (8.3%)	5 (8.3%)	1 (1.7%)	0 (0.0%)
Nausea	8 (13.3%)	5 (8.3%)	4 (6.7%)	0 (0.0%)	0 (0.0%)
Abdominal distension	1 (1.7%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	0 (0.0%)
Constipation	1 (1.7%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	0 (0.0%)
Investigations	8 (13.3%)	4 (6.7%)	4 (6.7%)	1 (1.7%)	0 (0.0%)
Blood creatinine increased	7 (11.7%)	4 (6.7%)	4 (6.7%)	0 (0.0%)	0 (0.0%)
Transaminases increased	1 (1.7%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	0 (0.0%)
Skin and subcutaneous tissue	7 (11.7%)	1 (1.7%)	5 (8.3%)	2 (3.3%)	0 (0.0%)
disorders					
Rash	5 (8.3%)	1 (1.7%)	3 (5.0%)	2 (3.3%)	0 (0.0%)
Pruritus	3 (5.0%)	0 (0.0%)	3 (5.0%)	0 (0.0%)	0 (0.0%)
Nervous system disorders	1 (1.7%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	0 (0.0%)
Headache	1 (1.7%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	0 (0.0%)

- <u>Auditory function</u>: Auditory tests were performed in 12 patients at baseline: 10 patients had normal test results whereas 2 patients had abnormal test results. But no auditory test results were available at 12 and 24 months of follow up.
- <u>Ophthalmology:</u> Ocular test results were reported for 10 patients at baseline and all had normal results. The ocular test results reported were however low and no test results were documented beyond baseline.
- <u>Weight:</u> The number of patients with weight measured varied from 59 patients at baseline to 18 patients at Month 24. Moreover, one child is included which affects the mean values. The

largest changes in weight from baseline were an increased weight of 10 kg and an 8.2 kg weight loss.

CHMP's comments:

The mean reduction SF is provided for the overall population (ie pediatric and adult). No specific analyses of the efficacy in paediatric patients have been conducted.

Available data on the only child included in this study were researched in tables and figures at the end of the report. Case description: a child, with a weight of 15kg at baseline and 19 kg M33. The indication for iron chelation is "other anemia". He was previously treated with deferoxamine intravenously, 5 to 7 infusions per week from 01 September 2005 to 18 December 2006, and with deferiprone from 20 July 2006 to 11 October 2006. On 18 December 2006, Exjade was started with a daily dose to 25 mg/kg, increased to 35 mg/kg at M18 then 40 mg/kg at M21 for insufficient chelation. Adverse events reported in this child were: Blood and lymphatic system disorders, splenomegaly (but for both the relationship with treatment was considered as unlikely), and severe gastrointestinal disorders (abdominal pain and vomiting) probably related to the treatment leading to a temporary discontinuation of deferasirox.

Available results over time for this child:

Test	ALT (µkat/L)	AST (µkat/L)	Creatinine (µmol/L)	GFR estimated with cystatine C (ml/min/1.73m ²)	Serum ferritin (µg/L)	Auditory and ocular tests	Exjade dosing (mg/kg)
Baseline	0.46	1.05	33		2993	Normal	25
M18			27		2668		35
M21	0.32	1.01	24	72	3484		40
M27	0.23	0.43	44	55	1453		40
M33	0.3	0.57	37	76	2004	Not performed	

Conclusions: Only child suffering from "other anemia" is included in this study, for which assessment of **safety of Exjade® is an objective**. Gastrointestinal adverse effects (= "adverse events probably related to the treatment") were reported in this child between M27 and M33 and lead to temporary discontinuation of Exjade. We also noted a decrease in GFR at M27. The dose of Exjade was increased to 40 mg/kg/j since M27. Auditory and ocular tests were performed at baseline but not after. Gastrointestinal and renal disorders were labelled in the SPC of Exjade®.

2.3.2.2.10. Study number CICL670ATR01: A prospective, non-interventional multicenter multinational registry of anemia patients requiring chronic transfusional therapy who are at risk for transfusional hemosiderosis

Description: In this study, data were collected on a multinational basis with the aim of creating an international registry to study the demographics and disease-management of chronic transfusional therapy-dependent anemia patients as well as iron overload and transfusional hemosiderosis.

Methods:

Objectives:

- **Primary objectives:** The primary objectives were to study the magnitude of the problem of iron overload in Turkey, Australia, Korea, Taiwan, Russia, Israel, Thailand, Malaysia, Hong Kong, Singapore, and China, gaining insight about this condition and the patterns of care regarding the use of iron-chelating therapy for transfusion-dependent anemias in this region. Other countries from the regions of Asia-Pacific, Middle East and South Africa could also be included into the registry.
- **Secondary objectives:** In a subset of countries/centers, some or all of the following were secondary objectives of this study:
 - To describe the demographics and the disease-management of newly diagnosed anemia patients requiring chronic transfusional therapy who were at risk for transfusional hemosiderosis
 - To investigate any correlation between clinical characteristics (including World Health Organization [WHO] classification and known prognostic factors) at inclusion, secondary iron overload due to transfusions or treatments received, and overall survival (censored at 3 years), time to leukemia progression, co-morbidities (including cardiac function), Karnofsky Performance Status (KPS) or quality of life.
 - To collect safety data on treatment with iron chelators, when applicable, including renal safety and liver safety.
 - To evaluate the severity of iron overload due to transfusion therapy in this world region.
 - To analyze the frequency of iron chelation therapy and regimens employed.
 - To analyze available compliance therapy with iron chelating therapy across different countries in the study region.
 - To create a regional knowledge base about iron overload, correlating the main findings with patients' country of origin, diagnosis, and local patterns of care.
 - To evaluate the frequency of clinical consequences of iron overload (cardiac disease, diabetes, growth failure, etc).

Study design: This was a prospective, non-interventional study. The registry was designed to

collect information about a large cohort of patients with newly diagnosed (within 12 months of the dater of diagnosis) anemia including myelodysplastic syndrome, aplastic anemia, Blackfan-Diamond or other anemias, and hemoglobinopathies such as beta-thalassemia, sickle-cell anemia and others requiring chronic transfusional therapy who were at risk of transfusional hemosiderosis. Patients were prospectively assessed in the context of existing registries represented within the region. Patients were observed until death, or for a maximum of 3 years.

Study period: 01-Dec-2008 to 29-May 2013.

Study population/Sample size:

A total of 69 centers involving 11 countries: Algeria (2 centers), China (13 centers), HongKong (1 center), Morocco (1 center), Russia (9 centers), South Africa (2 centers), South Korea (2 centers), Taiwan (6 centers), Thailand (7 centers), Tunisia (4 centers) and Turkey (22 centers) participated in the study.

The study population comprised: male and female patients over 2 years of age with newly diagnosed (within 12 months of the date of diagnosis) anemia including MDS (limited to patients with low or intermediate-I risk MDS), aplastic anemia, Blackfan-Diamond or other anemias and hemoglobinopathies such as beta thalassemia, sickle-cell anemia or others requiring chronic transfusional therapy.

This study was exploratory in nature; thus, the estimated sample size was not based on a statistical hypothesis, but on an estimation of the number of patients diagnosed with myelodysplastic syndrome, aplastic anemia, Blackfan-Diamond or other anemias, who required chronic transfusional therapy over a 12-month period, in centers considered large enough to register a sufficient number of patients with transfusional hemosiderosis and to perform a subgroup analysis.

The study was planned to involve approximately 62 sites. The expected number of enrolled patients at each site was 15; hence the expected sample size for the study was 800 to 1000 patients.

A total of 203/564 patients in total were treated with unspecified iron chelation therapy, including 28 paediatric patients

Treatments: In this non-interventional observational study, no study-specific treatment was given.

Outcomes/endpoints: Safety assessments consisted of all AEs, serious adverse events (SAEs), and pregnancies, regular measurements of vital signs, body weight, height, and an evaluation of the patient's KPS. If available, results from laboratory, radiological and cardiac assessments were collected.

Statistical methods: All analyses were performed on all patients as well as for patients aged \leq 18 years. All treatment-emergent AEs (TEAEs), including SAEs, were coded using MedDRA Version 16.0 to provide the System Organ Class (SOC) and preferred term (PT) for each AE. The incidence of all TEAEs was tabulated by SOC and PT. Relationship to treatment, severity of AE, and seriousness of AE were presented. Additional tables by maximum severity, outcome, action taken, and relationship to treatment was also presented. In all the tables and listings, AEs were categorized/grouped separately as AE onset before transfusion and after transfusion.

All laboratory data were converted to standard units, if not already converted during the data management process. The tabulation of laboratory data was to include the normal ranges for each variable. Each value was to be classified as falling above, below or within normal limit.

It was impossible to use a single central laboratory for all parameters and all patients; however, to avoid the issue of collecting hundreds of normal ranges, standard normal ranges were to be defined and applied for the purpose of statistical analysis.

Laboratory shift tables were presented for each parameter to assess the change from baseline values. The standard normal reference ranges were not available at the time of analysis, and therefore laboratory data have not been classified as falling above, below or within normal limit.

The tabulation of vital signs included the normal ranges for each variable. Each value was classified as falling above, below or within normal limit. Vital signs shift tables were presented for each parameter to assess the change from baseline values.

Results:

Recruitment/ Number analysed: Investigators at 69 sites in Algeria, China, Hong Kong, Morocco, Russia, Taiwan, Thailand, Turkey, Tunisia, South Africa, and South Korea entered a total of 564 patients, including 57 patients aged ≤18 years. Only 159 (28.2%) patients completed the study.

For patients aged \leq **18 years:** 15/57 (26.3%) patients aged \leq 18 years completed the study and 18 (31.6%) ended the study; for 24 (42.1%) patients \leq 18 years, disposition information was missing. The primary reasons for ending the study were lost to follow-up (11 [19.3%] patients and death (5 [8.8%] patients). No premature discontinuation for adverse events was recorded.

Baseline data: For patients aged ≤18 years: The pediatric patient population included similar proportions of males and females, with a mean age of 9.8 years (range 2 to 18 years). The majority of patients aged ≤ 18 years of age were White (54.4%) or Asian (31.6%) and most patients were recruited from Russia (17 [29.8%,] patients), China (15 [26.3%] patients) and Tunisia (10 [17.5%] patients). The majority had a diagnosis of aplastic anemia (30 [52.6%] patients), followed by betathalassemia major (9 [15.8%] patients), and other anemias (7 [12.3%] patients). Only 4 (7.0%) patients aged ≤ 18 years had a primary diagnosis of MDS. Overall, 36.8% (21/57) patients ≤ 18 years were assessed as having iron overload during the study. A greater proportion of patients aged ≤ 18 years receiving iron chelator (57.1% [17/28 patients]) had iron overload than patients aged \leq 18 years not treated with iron chelator (13.8% [4/29 patients]). Time-to-event variables were difficult to interpret due to the low numbers of patients ≤ 18 years of age. The majority of patients aged ≤ 18 years had a KPS score of 70 or above at each visit, and no overall difference in patient KPS scores was observed following treatment with an iron chelator or across the different countries who participated in the registry. The data from the early visits show that overall, drug therapy plus an erythrocyte transfusion and erythrocyte transfusion alone were being used as the treatment options of choice at study entry.

Concomitant diseases reported by $\geq 10\%$ of patients aged ≤ 18 years during at least one visit were: other (China, Morocco, Russia, South Africa, South Korea, Taiwan, Tunisia, Turkey), liver disease (Russia, South Korea), renal disease (Russia), diabetes mellitus (Turkey,) cardiac insufficiency (Turkey), and ophthalmic conditions (Russia, South Africa). No apparent differences were observed between countries with regards to the type or frequency of concomitant disease reported. Concomitant medications were taken by 28 (100%) patients aged ≤ 18 years receiving iron chelator (4 of whom were receiving drug therapy, 13 receiving erythrocyte transfusion and 12 receiving drug therapy and erythrocyte transfusion). Concomitant medications were taken by 25 (86.2%) patients aged ≤ 18 years not receiving drug therapy and erythrocyte transfusion). Overall, concomitant medications were taken by a higher proportion of patients aged ≤ 18 years receiving iron chelator treatment, and those receiving treatment with drug therapy and erythrocyte transfusion.

Efficacy results

According to the MAH, 29.4% (166/564) patients were assessed as having IOL during the study.

No specific analyses of the efficacy in paediatric patients have been conducted according to the iron chelation therapy.

Safety results: Overall, 18 (31.6%) patients \leq 18 years of age in the study reported AEs, and AE rates appeared lower in patients not treated with an iron chelator. Of the 28 patients \leq 18 years of age treated with an iron chelator, 14 (50%) reported at least one AE; 3 (10.7%) had AEs that were considered related to transfusion (erythrocyte and iron chelator transfusion). Of the 29 patients \leq 18 years of age not treated with an iron chelator, 4 (13.8%) experienced an AE; 1 (3.5%) patient had AEs that were considered related to transfusion. During the study 5 (8.8%) patients aged \leq 18 years died: 2/28 (7.1%) of whom were receiving iron chelator and 3/29 (10.3%) were not receiving iron chelator).

Five (8.8%) patients experienced SAEs, a similar number of which were reported by patients treated with iron chelator (3 [10.7%]) than not treated with iron chelator (2 [6.9%]). All SAEs reported in patients aged \leq 18 years occurred as single occurrences in the study. Hematology, clinical chemistry, vital signs, ECG and other investigations did not reveal any clinically relevant trends.

CHMP's comments:

In this observational study, all patients did not receive Exjade: 203/564 patients in total were treated with unspecified iron chelation therapy.

This study did not report any efficacy results presented separately according to the iron chelation therapy.

The collection of safety data was part of the secondary objectives of this study. Pediatric safety data were presented separately. This study included 57 pediatric patients, among them 28 were treated with iron chelators. Furthermore, only 17 patients/28 chelated patients had iron overload. However it was not possible for us to identify the drug used for iron chelation in these 28 children. Under these conditions, the pediatric safety data cannot be attributed to defensirox and are irrelevant.

2.3.2.2.11. Study number CICL670ATW01: Single-arm, Observational, Safety Evaluation of Exjade in Patients with Transfusion Hemosiderosis

Description: The study employs a prospective, single-arm, multi-center observational noninterventional trial design. The study was designed to collect the safety and efficacy data during 2 years treatment with Exjade® in target patient population of 200-300 thalassemia patients presenting with evidence of transfusion induced iron overload. Due to the non-comparative design of the study, randomization as well as blinding was not applicable.

Methods:

Objectives: To evaluate the safety profile of Exjade® in thalassemia treated for 2 years.

Study design: Single arm, multi-center, open-label, Phase IV, non-comparative, observational study

Study period: 13-Jan-2009 to 9-Dec-2011

Study population/Sample size: A total of 127 subjects in Taiwan.

Inclusion Criteria

1. Patients who were diagnosed of thalassemia with chronic iron overload due to blood transfusion that were either naïve or previously treated with chelation therapy agent(s).

- 2. Patients of either gender or age \geq 2 years old.
- 3. Patients or guardians had signed the inform consent form (ICF).

Treatments: Exjade® (deferasirox) tablets were administered according to package insert and requirement for transfusional overload. The Exjade® dose was recommended to be administered according to package insert once daily with starting dose of 20 to 30 mg/kg/day in patients with thalassemia. Treatment duration: 96 weeks. The starting Exjade dose for all enrolled patients was made according to individual investigator's judgement.

Outcomes/endpoints: Safety assessments performed in all patients consisted of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs) related to Exjade® use.

The assessment of safety was based mainly on the frequency of adverse events. A summary of clinically relevant toxic events, i.e., adverse events leading to death or are serious, those with a suspected relationship to study medication, those leading to study drug adjustment, interruption or discontinuation or adverse events requiring further medication or non-drug therapies were provided.

Hematology (included Hemoglobin, peripheral blood (WBC, differential, RBC, platelets)), blood chemistry (included serum creatinine, AST, ALT and urine exams) and vital signs (included height, body weight, sitting pulse and blood pressure) were followed. It was recommended that auditory and ophthalmic testing (including fundoscopy) should be performed before the start of Exjade® treatment and at regular intervals thereafter (every 6 months). A criteria for evaluation of efficacy was also collected: the percent change in serum ferritin level from baseline. Serum ferritin levels and value categories were summarized at baseline, each visit and end of study.

Statistical methods: The objectives of this trial were to evaluate the safety and change of serum ferritin of patients with administration of Exjade®. Exploratory analyses were performed using descriptive statistics. All statistical analyses were using a two-sided test at the 0.05 level of significance. Data from all study centers was pooled for central analysis.

Results:

Recruitment/ Number analysed: A total of 127 subjects were enrolled from 8 centers in this study. 105 (82.7%) patients completed the study and 22 (17.3%) withdrew from the study: Fourteen subjects (11.0%) withdrew their consents while 3 subjects (2.4%) terminated the study prematurely due to adverse events. The adverse events (drug related) led to study withdrawal included diarrhea, stomachache, and Fanconi syndrome. Two subjects (1.6%) discontinued the study because of unsatisfactory therapeutic effect, and 1 subject (0.8%) was lost to follow-up. One subject dropped out from the study due to death (acute heart failure) and one subject due to abnormal laboratory value (increased serum creatinine drug related).

Baseline data: The number of male and female was 64 and 63 of the study. The average age at enrollment was 21.94 years old, in the range of 2.04 to 69.83.

55 patients < 20 years were included: 31 males, 24 females, median age 15.8 years, 8 children (2-12 years old) and 47 adolescents (12-<20 years old). For patients < 20 years old: 47 had a beta-thalassemia major, 2 a beta-thalassemia intermedia and 6 an alpha-thalassemia. 50 (90.91%) of them have already been treated with deferasirox, 4 (7.27%) with deferoxamine and deferiprone and 1(1.82%) with deferiprone. The most frequently reported medical condition was osteoporosis (9 – 16.36%), hypogonadism (4 – 7.27%), rhinitis allergic (4 – 7.27%), growth retardation (3- 5.45%), diabetes mellitus (2- 3.63%), splenomegaly (2 – 3.63%), deafness neurosensory (2 -3.63%)...

Exjade was the main last chelation therapy before enrolment (50). Duration of receiving transfusion therapy was 13.16 ± 4.45 years, ranging from 1 to 19 years. During the last year, the mean transfusion number was 19.02 ± 5.14 while the mean total amount of transfusion during the last year was 10993.8 ± 4230.2 mL. No data about initiation dose or regimen dose or duration of deferasirox treatment was presented separately for paediatric population.
Efficacy results

Among the 55 subjects with age less than 20 years old, the geometric mean ferritin level at baseline and at month 24 was 1567.7 ng/ml and 1363.4 ng/ml, respectively. The geometric mean ratio had significant changes at month 2, 4, 7, 8, 9, 16, 17, and month 18, but the geometric mean ratio at month 24 was 0.93 without significance (p=0.3831). The number of increase and decrease of ferritin category were the same (11 subjects) at month 24. The percentage of subjects with ferritin level less than 1000 ng/mL reduced from 34.55% at baseline to 27.66% at month 24.

By contrast, *for the 72 subjects aged 20 or more*, the geometric mean ferritin level changed from 2622.8 ng/ml at baseline to 1672.3 ng/ml at month 24. Significant changes were obtained for the geometric mean ratio at month 2, 4, 5, and since month 7. The geometric mean ratio at month 24 was 0.69 with significance (p<0.0001). For the 72 subjects with age greater than or equal to 20 years old, the number of reduction (23 subjects) was more than that of increase (9 subjects) in ferritin category. The percentage of subjects with ferritin level less than 1000 ng/mL increased from 15.28% at baseline to 27.59% at month 24.

For all subjects, the geometric mean of ferritin level was 2098.8 ng/ml at baseline and decreased to 1526.2 ng/ml at month 24; the geometric mean ratio from baseline was 0.92 at month 2 with statistically significance (p=0.0033) and thereafter significant reduction was observed until the end of study for all subjects; at month 24, the geometric mean ratio was 0.79 with p<0.0001. At month 24, ferritin category were increased for 20 subjects while 34 subjects decreased the ferritin category from baseline. The percentage of subjects with ferritin level less than 1000 ng/mL increased from 23.62% at baseline to 27.62% at month 24.

These results (change of geometric mean ferritin level, number of subjects who improved the ferritin category versus those who worsened, change of percentage of subjects with ferritin level less than 1000 ng/mL) improved more apparently in patients aged 20 or more than patients less than 20 years. The geometric mean change from baseline is presented as Figure below (Summary of Geometric Mean Profile of Ferritin Level (ng/mL)).



For all subjects, the study also showed that median change in serum ferritin level was related to the baseline ferritin level and mean Exjade dose. Baseline ferritin less than 1000 ng/ml with mean Exjade daily dose of 20 to 25 mg/kg led to slightly increasing serum ferritin, baseline ferritin 1000 to 2500 ng/ml with mean Exjade daily dose of 30 mg/kg led to slightly decreased serum ferritin, whereas baseline ferritin greater or equal to 2500 ng/ml with mean Exjade daily dose of 35 mg/kg led to apparent reductions of serum ferritin values.

Exjade produced a reduction in serum ferritin level that was related to the dose administered. Baseline dose of less than 20 mg/kg were able to maintain serum ferritin, whereas a dose between 20 to 30 mg/kg slightly decreased serum ferritin and a dose of greater than or equal to 30 mg reduced serum ferritin level apparently.

Safety results

During the study period, 35 patients (27.56%) reported at least one adverse event related to Exjade®. Drug-related AEs led to study drug dosage adjustment, those required further medication, and nondrug therapy were in 21 (16.54%), 8 (6.30%), and 0 (0.00%) patients, respectively.

The most frequently experienced drug-related adverse events included abdominal pain upper (7 patients, 5.51%), diarrhoea (7 patients, 5.51%), gastritis (6 patients, 4.72%), abdominal discomfort (4 patients, 3.15%), abdominal pain (3 patients, 2.36%), and nausea (3 patients, 2.36%). Data were not presented by age groups.

There were 7 subjects (5.51%) experienced drug-related serious adverse events, which 5 were aged under 20 years:

- Acute gastroenteritis in a young adult patient , with erosions and ulcer scar over gastric fundus and cardiac portion were observed during panendoscopy
- A Fanconi syndrome in a young adult patient ; Exjade was permanently discontinued.

- A liver abscess in an adolescent
- An urticaria with fever in an adolescent
- A transaminases increase in an adolescent, which was assessed as suspected related to study drug and caused temporarily interruption of Exjade®.

For laboratory profile, statistically significant changes were seen, but the changes were not clinically meaningful and most of them resulted from underlying disease status and adverse events. However, two subjects suffered from ALT elevation which was assessed as suspected related to study drug and one of them reported SAE and interrupted the usage of Exjade® temporarily. Besides, elevated serum creatinine was reported as suspect adverse event in 3 subjects and led to study drug dosage adjustment or temporary interruption. Deafness neurosensory was reported as suspected adverse event in one subject (0.8%).

CHMP's comments:

Efficacy data

The interpretation of the presented data is limited, and the results only have an observational value, due to:

- The lack of paediatric results being analyzed separately,

- The design of the study: open-label, non-randomized, non-controlled with main limitations including potential selection bias, missing data and lack of internal validity.

As a reminder, the MAH submitted this clinical study report in the context of article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. A clear description of patient exposure and dose interruption data done by age group in order to compare paediatric and adult population would have been expected.

Regarding these elements no conclusion in terms of efficacy of deferasirox in paediatric population can be drawn. On the contrary, from the data presented above, efficacy in reducing iron overload appears to be lower than in adult population.

In addition, for the overall population, the data suggest that the level of reduction in serum ferritin level was proportional to the baseline ferritin level and the mean Exjade dose. At low baseline ferritin (less than 1000 ng/ml) and lower Exjade daily dose (20 to 25 mg/kg), serum ferritin is slightly increasing. The apparent reduction of serum ferritin values was observed with baseline ferritin greater or equal to 2500 ng/ml and a mean Exjade daily dose of 35 mg/kg.

A subgroup analysis allowing to assess the relationship between ferritin level and exjade dose in the pediatric population should be provided.

Safety data

Pediatric safety data were not presented separately.

Search in tables retrieves pediatric data in the Table 20a, Summary of drug related adverse events: 17 patients < 20 years experienced drug adverse effects, 12 mild and 5 severe.

- Severe adverse events: Fanconi syndrome (1), diarrhoea (1), liver abscess (1), alanine aminotransferase increased (1), urticaria (1)

- Mild or moderate adverse events: deafness neurosensory (1), gastrointestinal disorders (7: abdominal discomfort, upper abdominal pain, diarrhea, ulcer gastric, gastritis), hepatobiliary disorders (1 hepatitis), Infections and infestations (2 gastroenteritis), investigations (7: alanine aminotransferase increased, blood amylase increased, blood creatinine increased), Skin and subcutaneous tissue disorders (1 rash).

Except for liver abscess and blood amylase increase, all adverse events reported were expected and labelled.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion: Deferasirox is an iron chelator indicated for long-term use in the treatment of chronic iron overload due to blood transfusions in pediatric patients from 2 years. The first worldwide marketing authorization for deferasirox was received on 02-Nov-2005 and it is currently available in 118 countries including the 28 Member States of the European Union. In this context, the recording of safety data about immediate tolerability but also about the long-term safety is necessary.

In this report, all the studies submitted by Novartis for deferasirox were conducted since February 2006 and the latest was completed in May 2013. We remind the MAH that, according to the EMA website, the MAH should submit the paediatric studies <u>within six months of its completion</u> and irrespective whether or not it is part of a PIP (completed/or not yet completed) or whether it is intended for submission later on as part of a variation, extension or new stand-alone marketing-authorisation application or not. For future studies including paediatric data, the MAH should comply with the EMA guideline in terms of submission dates.

These 15 studies that enrolled pediatric patients (defined as patients aged < 18 years) were submitted: 4 interventional and 11 observational. None of them was designed specifically to collect pediatric safety data. However according to the guideline for Article 46, "*studies should be submitted regardless of the region where they performed, the aim, outcome, population studied or indication*". In interventional studies, 66 pediatric patients were enrolled on 223 total patients. In observational studies, 396 pediatric patients were enrolled on 7709 total patients. Therefore, the proportion of paediatric patients enrolled in the above-mentioned studies varied from 1.3 % to 41.9 %.

Efficacy results

Various parameters were used in the interventional or non-interventional presented studies to measure efficacy, such as change from baseline in regular time intervals in cardiac iron overload (by using myocardial MRI T2*), cardiac function endpoints (LVEF), liver iron concentration (by using liver MRI T2*), serum ferritin, transferrin saturation. These are acceptable variables. Two studies did not report any efficacy information (CICL670BR01 and CICL670TR01).

In the four interventional studies, various efficacy results were presented but the results on the paediatric patients were not presented separately. Similarly, in the 11 non-interventional studies identified, various efficacy results were presented but only limited efficacy data on paediatric patients were analyzed and reported separately: with the exception of four studies (CICL670AGR01, CICL670AIC02, CICL670ATR01 and CICL670ATW01), no specific analyses of the efficacy in paediatric patients have been conducted.

Only two studies are therefore considered to be relevant for the analysis of efficacy in paediatric patients: CICL670AGR01 and CICL670ATW01, for the reasons explained above (all patients did not receive Exjade in CICL670AIC02 and CICL670ATR01, without results provided separately according to the iron chelation therapy).

The interpretation of the presented data in both studies (CICL670AGR01 and CICL670ATW01) is limited, and the results only have an observational value, due to:

- The modest number of children enrolled (24 in CICL670AGR01 and 55 in CICL670ATW01),

- The lack of paediatric results being analyzed separately,

- The design of the studies: open-label, non-randomized, non-controlled with main limitations including potential selection bias, missing data and lack of internal validity.

As a reminder, the MAH submitted this clinical study report in the context of article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. A clear description of patient exposure and dose interruption data done by age group in order to compare paediatric and adult population would have been expected.

Regarding these elements no conclusion in terms of efficacy of deferasirox in paediatric population can be drawn. On the contrary, from the data presented above, efficacy in reducing iron overload appears to be lower than in adult population.

Safety results

Post-marketing surveillance studies were available: A1401 (Japan), ADE-04 and ADE-05 (Germany) and AKR01 (Korea). In some studies (AGR01, ASE01 and ATW01), the evaluation of the safety of treatment with Exjade was part of the primary objectives. The assessment of the safety and tolerability or acceptability of deferasirox was included in the secondary objectives for studies number: AAU01, ABR03, ARU01, AUS04, ATR01. The evaluation of safety data was not planned in the latest studies: A2418, ABR01, AIC02.

In the twelve studies with available safety data, separate pediatric safety results were provided for three studies only (A1401, AGR01 and ATR01) and for a limited number of patients with different cut off of age: 40 patients under 15 years in A1401 and 24 less 16 years for AGR01 and 57 patients aged ≤18 years for ATR01. Furthermore regarding the ATR01, only 28 pediatric patients / 57 were treated by iron chelator, but without specification of the used drug. The largest number of pediatric patients (209 patients) was recorded in the AKR01 study but only the synopsis was submitted and no detail about safety data was available. Finally, in the global pediatric population we found only 70 drug related adverse events and 10 serious drug related adverse events. The drug related adverse events (DRAEs) reported in the pediatric population were: gastrointestinal disorders, renal disorders, investigations disorders, liver disorders, skin and subcutaneous tissue disorders, musculoskeletal and connective tissue disorders. Fanconi syndrome is found in two pediatric patients in two different studies (ATW01, AUS04). We noticed that no data is provided about the follow up of ear and eye disorders in children, either about growth and sexual development disorders (excepted in study number AGR01). These sparse safety data did not found unexpected and unlabeled adverse effects (excepted one case of rectal prolapse and liver abscess and blood amylase increased), but the number of patients was too small to detect rare and unexpected adverse drug reactions. This drug is now marketed for 10 years and no pediatric cohort study was performed by the MAH. In these conditions, the submitted data are too limited to describe the pediatric safety profile of deferasirox and to justify an amendment of the product information.

A rapid research in the medical literature is found that some authors are interested to the pediatric safety of deferasirox:

- renal safety in child [*Chuang GT, et aL. Transfusion-dependent thalassemic patients with renal Fanconi syndrome due to deferasirox use. Nephrology (Carlton). 2015*],
- endocrine function and bone disease during long-term chelation therapy with deferasirox in patients with Beta-thalassemia major [*Casale M et aL. Endocrine function and bone disease during long-term chelation therapy with deferasirox in patients with* β*-thalassemia major. Am J Hematol.* 2014],
- or efficacy and safety of the combination of two oral chelators deferasirox (DFX)/deferiprone (DFP) over deferoxamine.(DFO)/deferiprone in severely iron overload young beta-thalassemia major patients [*Elalfy MS*, et al. Efficacy and safety of a novel combination of two oral chelators deferasirox/deferiprone over deferoxamine/deferiprone in severely iron overloaded young beta thalassemia major patients. Eur J Haematol. 2015],
- follow up for a period of 36 months of the first 50 children (age 2-18 yrs) with thalassemia major who started deferasirox [*Dhamija M et aL. Deferasirox in Indian children with thalassemia major: 3 years experience. Indian J Med Paediatr Oncol. 2013*]...

These topics and studies are interesting and must be investigated by the MAH to progress in the description of the safety profile in children: to specify the pediatric renal or hepatic safety, the occurrence of eye and ear disorders in chronically treated children and to evaluate the long-term safety on the growth and the endocrine function (although the latter are also affected by iron overload), and the combination of iron chelators.

In conclusion, this drug is on the market since 10 years without any major changes in formulation and use. An extension of indications was approved in EU in November 2012 for the treatment of chronic iron overload requiring chelation therapy in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older. This new indication included also pediatric population. The submitted safety data are old and should have already taken into account during the regular assessment of PSURs. The data provided by the MAH in this report are insufficient and inadequate to describe specifically the safety profile in the pediatric population.

Recommendation

Not fulfilled:

Firstly, we remind that, according to the EMA website, the MAH should submit the paediatric studies **within six months of its completion** and irrespective whether or not it is part of a PIP (completed/or not yet completed) or whether it is intended for submission later on as part of a variation, extension or new stand-alone marketing-authorisation application or not. For future studies including paediatric data, the MAH should comply with the EMA guideline in terms of submission dates.

Secondly, based on the data submitted, the safety profile and the efficacy of Exjade in pediatric population cannot be correctly analysed as the MAH has not distinguished the paediatric data separately for subgroups of children and adolescents as part of this procedure. The MAH should consider such presentation for future studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended.

It would be necessary to request to the MAH to provide pediatric results for safety and for efficacy separately <u>for all studies</u> and distinguish safety and efficacy data for subgroups of children and adolescents as part of this procedure. However, the number of children enrolled are too small to conclude in most studies. Therefore, in adopting a pragmatic approach, we consider that the MAH should provide an analysis specifically for the paediatric population

- From study CICL**670ATW01**, for efficacy data : a subgroup analysis allowing to assess the relationship between ferritin level and exjade dose in the pediatric population should be provided.
- from study CICL670AKR01 for safety data : a subgroup analysis with children and adolescents. Indeed, this study contains the largest population of children (n=209 children aged between 2 and <12 years-old and probably more between 12 and 18 years-old).

These efficacy and safety data in paediatric population are interesting to be known (see section IV "Additional clarifications requested").

Additional clarifications requested

Based on the data submitted, the MAH should provide an analysis specifically for the paediatric population

- From study CICL**670ATW01**, for efficacy data : a subgroup analysis allowing to assess the relationship between ferritin level and exjade dose in the pediatric population should be provided.
- from study CICL670AKR01 for safety data : a subgroup analysis with children and adolescents. Indeed, this study contains the largest population of children (n=209 children aged between 2 and <12 years-old and probably more between 12 and 18 years-old).

Also, the MAH should commit to

- 1) comply with the EMA guideline in terms of submission dates for future studies including paediatric data
- 2) consider to present paediatric data (efficacy and safety) separately for each future studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended.

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

MAH's responses (submitted in December 2015)

Question 1:

Based on the data submitted, the MAH should provide an analysis specifically for the paediatric population

• From study CICL670ATW01, for efficacy data: a subgroup analysis allowing to assess the relationship between ferritin level and Exjade dose in the pediatric population should be provided.

MAH's Response

CICL670ATW01 is a prospective, single-arm, multi-center observational non-interventional trial, to collect the safety and efficacy data during 2 years treatment with Exjade thalassemia patients

presenting with transfusion induced iron overload. Patients were treated with deferasirox in accordance with the local deferasirox prescribing information. The study was conducted in Taiwan from 13-Jan-2009 to 9-Dec-2011 and a total of 127 subjects were enrolled from 8 centers.

Of those, 40 (31.4%) were paediatric patients with mean (SD) age of 13.5 (3.9) years at the study entry. The majority of the patients were diagnosed with Beta-thalassemia major 34 (85%), followed by Alpha-thalassemia 5 (12.5%) and Beta-thalassemia intermedia 1 (2.50%). Mean (SD) transfusion number during the last year prior the enrollment was 18.05 (4.89). The mean dose was 25.2 mg/kg /day and the majority of the patients (70%) were treated with <30 mg/kg/day.

At the study entry there were 14 (35%) patients who had serum ferritin (SF) <1000 μ g/L (mean (SD) SF 776.1 (150)), 16 (40%) with serum ferritin between 1000 and 2500 μ g/L (mean (SD) SF 1718.9 (455.1)), and 10 (25%) patients with serum ferritin greater than 2500 μ g/L (mean (SD) SF 3804.2 (1661.2)).

Overall in the paediatric population, serum ferritin level decreased from mean (SD) baseline of 1910.2 (1456.2) μ g/L to 1568.3 (1057.4) μ g/L at month 24. For 12 (30%) patients treated with <20 mg/kg (mean dose 15.8 mg/kg), the mean (SD) serum ferritin was reduced from 1338.8 (915.1) μ g/L at baseline to 1107.2 (624.1) μ g/L at the end of study. For 16 (40%) patients treated with 20-30 mg/kg (mean dose 25.5 mg/kg) the mean (SD) serum ferritin decreased from 2021.6 (1177.0) μ g/L at baseline to 1630.6 (1257.1) μ g/L at the end of study; whereas for 12 (30%) patients receiving >30 mg/kg (mean dose 34.3 mg/kg), the mean (SD) serum ferritin was reduced from 2333.3 (2054.9) μ g/L to 1896.0 (1004.4) μ g/L. It appears that all three deferasirox dose categories showed a reduction in serum ferritin levels. Notably, changes in mean (SD) serum ferritin from baseline to the end of study were similar in patients receiving 20 to 30 mg/kg/day [-372.8(1494.3)] and > 30mg/kg/day[-446.3(1568.1)] whereas a change in patients receiving <20 mg/kg/day was [- 76.0(1182.2)]

When the response was analyzed by serum ferritin levels at baseline: <1000 μ g/L, 1000 –2500 μ g/L and ≥2500 μ g/L, the greatest numerical reduction in mean (SD) serum ferritin from 3804.6 (1661.2) μ g/L at baseline to 2091.2 (1693.4) μ g/L at the end of study was observed in the patients who entered the study with ≥2500 μ g/L (Figure 1-1). This was achieved with mean (SD) dose of 28 (7.9) mg/kg/day.

Figure 1-1 Serum ferritine levels at baseline ≥2500 µg/L

Baseline >=2500 (n=41)



Furthermore, in patients who entered the study with baseline serum ferritin levels between 1000 and 2500 μ g/L, the mean (SD) serum ferritin level 1719 (897.6) μ g/L remained unchanged at the study end. The mean (SD) dose for this category was 29.7 (8.5) mg/kg/day. On the contrary, patients with baseline serum ferritin level <1000 μ g/L who were treated with a mean (SD) dose 20.9 (6.6) mg/kg/day had a slight increase in mean (SD) serum ferritin from baseline 776.1 (150) μ g/L to 1086.1 (528.4) μ g/L at the study end. This suggests that a dose increase of defensirox may be needed to maintain serum ferritin below a recommended level of 1000 μ g/L.

Of note, serum ferritin is an acute state reactant and some non-clinically significant fluctuation may be observed between visits. Statistical Analysis Tables are provided in [Appendix 1].

In summary, these findings should be interpreted with considerable caution, as they derived from an observational study in which the number of patients in each category is rather small to draw a meaningful conclusion on a relationship between serum ferritin and deferasirox dose. Additionally, compliance was not monitored in this study and some serum ferritin levels were not collected at the study visit, making the interpretation of the findings challenging.

CHMP's comment

The MAH provided a subgroup analysis to assess the relationship between ferritin level baseline and Exjade dose in the pediatric population. However, activity of deferasirox remains unclear in patients who had SF <1000 μ g/l at baseline. The MAH suggest that a dose increase of deferasirox may be needed to maintain SF below a recommended level of <1000 μ g/l. The design of this study could not allow to draw firm conclusions about the interest of a deferasirox treatment and/or the dose needed in this study population. However, new efficacy data in children aged 2 to less than 6 years at enrolment with transfusional hemosiderosis treated with deferasirox will be assessed in the frame of the variation II-48.

Question 2:

Based on the data submitted, the MAH should provide an analysis specifically for the paediatric population from study CICL670AKR01 for safety data: a subgroup analysis with children and adolescents. Indeed, this study contains the largest population of children (n=209 children aged between 2 and <12 years-old and probably more between 12 and 18 years-old).

MAH's Response

CICL670AKR01 is an open-label, multicenter, single-arm, observational post-marketing surveillance conducted for 6 years, from 31 March 2006 to 30 March 2012. Study doctors enrolled patients with transfusion dependent hemosiderosis who had received at least one dose of defensirox.

Background:

A total of 1,579 patients were enrolled in the study. Of those, 363 (23%) were pediatric patients <18 years of age. The mean age of the paediatric patients was 9.51 ± 4.7 years. Within this population, underlying diseases were reported in 264 patients (72.7%). The majority of the patients were diagnosed with other neoplasms 129 (35.5%), followed by other diseases, acute lymphocytic leukemia (ALL) and aplastic anaemia (AA) [58 (16%), 39 (10.7%), and 34 (9.4%)] respectively ([Appendix 2] Table 13.1).

Within the paediatric population, 309 (85.1%) patients were treated with concomitant medication. The most commonly used medication by class was anti-infectives for systemic use (199; 64% patients), followed by antineoplastics agents (143; 46.2% patients), and cardiovascular system and blood and blood forming organs (134; 43.3% patients). During the study, 152 (41.8%) pediatric patients discontinued treatment with deferasirox. Of those, 75 (49.3%) patients discontinued due to reasons reported as 'others", 44 (28.9%) due to "adverse events", 18 (11.8%) due to "improvement", 8 (5.3%) due to "lack of efficacy" and 8 (5.3%) due to "lost to follow up". Although, the treatment discontinuation was somewhat high, one should not exclude the impact of confounding factors including underlying hematological malignancies and concomitant use of chemotherapy.

The mean daily dose of deferasirox was 635.92 ± 333.06 mg. Most of the patients (41.9%) were treated with a daily dose between 500 mg and 1000 mg. The overall mean duration of exposure was 130.1 \pm 133.2 days, with 263 (72.5%) patients receiving at least 6 months of treatment.

For 344 evaluable paediatric patients, the mean serum ferritin was reduced from 2,346 μ g/L at baseline to 1,670 μ g/L at the end of study. The mean decrease of 676.6 μ g/L was statistically significant (p < 0.001).

Overall adverse events

Overall, there were 175 (48.2%) pediatric patients with at least one adverse event (AE) regardless of study drug relationship. A total of 372 events were experienced by these 175 pediatric patients. The most commonly affected primary SOCs were Blood and lymphatic system disorders (83 patients; 22.9%), Gastrointestinal disorders (48 patients; 13.2%) followed by Investigations (37 patients; 10.2%). The most frequently AEs reported by \geq 3% of patients by preferred term were febrile neutropenia 62 (17.1%), neutropenia 29 (8%), alanine aminotransferase increased (ALT) 24(6.6%),

aspartate aminotransferase increased (AST) 22(6.1%), vomiting 19 (5.2%), rash 13 (3.6%), nausea, pyrexia and diarrhea (12; 3.31% each), upper respiratory tract infection 11(3%). Notably, 163 (93.1%) of 175 patients with AEs were receiving concomitant medication. Of those, 112 (68.7%) patients were treated with antiinfective and systemic use, 96 (58.7%) were treated with antineoplastic agents and 94 (57.7%) were treated with cardiovascular system and blood and blood forming organs ([Appendix 2] - Table 34).

The majority of AEs were classified as mild in severity (263 events, 70.7%), followed by moderate (102 events, 27.4%) and severe (7 events, 1.9%) ([Appendix 2] - Table 39). Of the total 372 reported AEs, 280 (75.3%) were assessed as unlikely to be related to the study drug, 68 (18.3%) with possible relation to the study drug and 13 (3.5%), including vomiting 6, rash 3, gastrointestinal disorder (not specified), blood creatinine increased, liver function test abnormal, metabolic acidosis (1; each), with probable/likely relation. Only one (0.27%) AE, rash, was assessed as being certainly related to the study drug. Causality assessment of 10 (2.7%) AEs were conditional/unclassified. ([Appendix 2]- Table 45 and 46)

The most common actions taken for AE management were Medical/Non-medical treatment 225 (60.5%), permanent discontinuation 44 (11.9%) and dose modification/temporary discontinuation 29 (7.8%). Of note, 54 (14.5%) patients with AEs did not require any actions. ([Appendix 2]- Table 41).

Importantly, resolution was reported for the great majority of the AEs, 340 (91.4%). Whereas the resolution was not reported by the end of observation for 11 AEs (2.9%), including gastrointestinal disorder (not specified), blood creatinine increased, febrile neutropenia, encephalitis, tumour pain, ear pain, retinal haemorrage, deafness neurosensory, diabetes insipidus, and proteinurea (2). Of note, 17 (4.6%) AEs were reported as improving at the study end. Four (1.1%) AEs resulted in fatality in three patients during the study ([Appendix 2] - Table 43 and 44). For details please refer to section "Death".

All cases of febrile neutropenia 96 (25.8%) and neutropenia 34 (9.1%) were assessed by the investigators as unlikely to be related to the study drug. The majority of febrile neutropenia and neutropenia were assessed as mild in severity; 69 (71.8%) and 32 (94.1%) respectively.

Of all cases, only one of febrile neutropenia was not resolved at the study end. Importantly, considering underlying diseases (e.g. ALL) it is not uncommon to observe neutropenia or febrile neutropenia in this population, especially in patients with hematologic malignancies.

Moreover, the effect of concomitant use of antineoplastic agents cannot be rule out since neutropenia, resulting from cytotoxic chemotherapy is the most common risk factor for severe infections in hematological malignancies.

All cases of elevated ALTs 27 (7.2 %) and ASTs 24 (6.4%) were assessed as mild and moderate in severity but one patient demonstrated one ALT and one AST AE which were assessed as severe. The majority of ALT 14 (51.9%) and AST 13 (54.7%) increased AEs were assessed by the investigators as unlikely to be related to the study drug. For the rest of these events, possible relationship to deferasirox was reported. At the study end, greater majority of patients with ALT and AST increased AEs recovered from the events and only 3 of each were reported as being in a recovering stage. No patients with ALT and AST increased AEs were reported by the investigators as not being recovered from the events ([Appendix 2] - Table 40, 44 and 46).

Of total 13(3.4%) cases of rash, 12 were assessed by the investigators as mild and one as moderate in severity. Of those, 5 events were assessed with possible relationship to the study drug, 4 with unlikely relationship to the study drug, 3 with probable/likely and only one case was assessed as having a certain relationship to the study drug. Importantly, all patients recovered from the event but one who

was in a recovering stage at the study end. Of total 175 patients with AEs, 65 (17.9%) were reported to have at least one AE suspected to be related to deferasirox, referred to as Adverse Drug Reactions in the study report. Within the study, total of 92 events were experienced by 65 patients. Of those, most frequent AEs reported by >2% of patients were 12(3.3%) vomiting, 11(3%) ALT increased, 10 (2.8% each) AST increased and nausea, and 9 (2.5%) rash.

Overall, 104 (28.6%) of pediatric patients experienced at least one AE during the study that was "unexpected", meaning that the event term was not specifically listed in the applicable reference safety information. The most commonly affected primary system organ classes were Blood and lymphatic system disorders (63 patients; 17.4%), followed by Infections & infestations (26 patients; 7.2%) and Respiratory, thoracic and mediastinal disorders (11 patients; 3%). The most frequent unexpected AEs (\geq 3% of patients) by preferred terms were febrile neutropenia 62 (17.1%), and upper respiratory track infection 11 (3%). There were 184 of these events in these cases, of which 14 AEs (3.86% of the total event count in the paediatric population) were suspected to be related to study drug, due to a "possible" relationship: otitis media, 2 blood urea increased, 2 cough, 2 upper respiratory infection, paraesthesia, weight decrease, decrease appetite, folliculitis, hyperbillirubinaemia, metabolic acidosis, blood bilirubin increased. Eleven were classified as mild and three (otitis media, weight decrease and metabolic acidosis) as moderate in severity, and all patients recovered from the events. None of these events were reported to be certainly related to the study drug.

One of them (otitis media) was reported as an SAE, see below.

SAE:

Serious adverse events (SAEs), irrespective of relationship to deferasirox treatment, were reported in 18 (4.96%) patients. Overall, these 18 patients experienced 21 SAEs during the study. The most commonly SAEs were in the following System Organ Class (SOC): Infections and infestations (7 patients; 1.9%) patients, General disorders and administration site conditions (4 patients; 1.1%) patients, followed by Gastrointestinal disorders (3 patients; 0.8%) patients. The rate (1; 0.28%) at which SAEs by preferred terms occurred was consistent for all reported events but for disease progression (2; 0.55%). For details on SAEs' rate and frequency by preferred terms please refer to the [Appendix 2] - Table 20.

All SAEs, but one (0.28%) Otitis Media were assessed as unlikely to be related to the study drug. The case of Otitis Media was reported as Serious Adverse Drug Reaction (SADR) with a possible relationship to the study drug. Of note, the patient recovered after treatment interruption and subsequently continued deferasirox.

The majority of SAEs were classified as moderate in severity ([Appendix 2] - Table 21) and all patients recovered except for three who died during the study (see details below).

Deaths:

Three pediatric patients died during the observational study period. None of the deaths were suspected to be related to deferasirox. Brief narratives of the cases are provided below. Each of the three patients had underlying malignant tumours. In the third case, the cause of death was septic shock and there is limited information on underlying risk factors and treatment dates with deferasirox. For details please refer to [Appendix 3].

□ A paediatric patient, treated with deferasirox, had a medical history of Ewing's sarcoma. The patient was also treated with concomitant medications included etoposide and thiotepa. Multiple metastatic lesions were reported with thoracic and brain MRI. The outcome of the Ewing sarcoma disease

progression was reported as death. Deferasirox treatment was stopped approximately two weeks prior to the fatal event. The causality of the event was not suspected to be related to deferasirox.

□ A paediatric patient who had a medical history of malignant peripheral nerve sheath. The patient was treated with deferasirox as well as concomitant medication included carboplatin and ifosfamide. On Positron emission tomography (PET), malignant mass in the mediastinal was noted, suggesting disease progression. The patient died approximately 2 months later after deferasirox treatment was discontinued. The causality was reported as not suspected to deferasirox.

☐ An paediatric patient with medical history that included neuroblastoma received deferasirox for iron overload. On an unknown date, gram-negative rods were isolated in blood culture. Patient developed septic shock and died due to the event. During the event the patient was treated with an inotropic drug. The causality for the event was assessed as not suspected to deferasirox by the investigator.

Summary:

According to the MAH, the limitation of this study was related to its design as a single arm observational study which did not impose a therapy protocol or diagnostic/therapeutic interventions. Moreover, some of the clinical data and details of underlying diseases were not available for collection.

Less than half of the 368 pediatric patients in the study (48.2%) experienced an AE during the observation period. Overall, the majority of AEs were mild in severity and were assessed by the investigators as unlikely to be related to the study drug.

Fourteen patients had AEs suspected to be related to study drug and "unexpected" according to the reference safety information, but these were mostly mild in severity and the relationship to deferasirox was not conclusive.

Importantly, greater majority of patients who presented with AEs, including ALT and AST increased, recovered or were recovering from the events within the study. No renal safety concerns were observed in this observational study. Only one patient with creatinine increased did not recover by the end of the study period. None of the events of febrile neutropenia and neutropenia were related to the study drug.

It is also important to highlight that causality of these events should be interpreted with caution as the presence of underlying disease and its complications as well as concomitant administration of multiple medications make the assessment is rather challenging. Thus, one cannot be ruled out the effect of mentioned confounding factors on these findings. Of all SAEs, only one was reported to be related to the study drug. Importantly, the event resolved after treatment interruption and patient continued the treatment. No death was suspected to be related to deferasirox as assessed by the investigator. Overall, the safety profile of paediatric patients treated with deferasirox was consistent with previous reports.

CHMP's comment

This observational study contains only descriptive and non comparative data in real life.

As requested, the MAH has provided a safety analysis in the paediatric population enrolled in this observational study. The total number of paediatric patients is 363 *(or 368 in the MAH summary??)* from 2 to 17 years-old (mean 9.5 +/- 4.72)).

A total of 175 paediatric patients reported 372 AEs including 21 SAEs in 18 patients (mainly infections, general disorders and GI disorders).

Fatal cases:

A total of 3 fatal cases were reported in the paediatric population of this study: 2 due to underlying disease progression (metastatic lesions/encephalopathy in a context of Ewing's sarcoma and malignant peripheral nerve sheath) and one due to septic shock. In this last case, the circumstances of occurrence of septic shock were not enough detailed to conclude on the role of Exjade. One case of otitis media was considered as possibly related to deferasirox (compatible time to onset : 15 days, positive dechallenge). However, it seems that no recurrence of otitis media was noted after reintroduction of Exjade at the same dose. This case contains too scarce information to conclude on this case.

Among the 184 unexpected AEs (in 104 patients), the main events reported are febrile neutropenia (96 AEs) followed by upper respiratory tract infection (11 AEs, all manageable by medical/non medical treatment) and cough (6 AEs). A total of 44 patients (29%) discontinued permanently Exjade due to AEs (mainly due to liver or renal function tests abnormal and GI disorders).

The overall safety profile seems to be consistent with the known safety profile of Exjade and complications of underlying conditions. However, we consider that additional analysis are requested to accurately assess the data from paediatric population as this study contains the largest population of children (n=209 with children aged between 2 and <12 years-old) observed in real life conditions:

Febrile neutropenia

All events of febrile neutropenia (96 AEs) and neutropenia (34 AEs) were assessed by the investigator as unlikely related to deferasirox. Overall, 74 patients (including 62 paediatric patients) experienced one or several episodes of neutropenia (mainly were considered as mild – 71.8%). None are reported as serious.

All cases of febrile neutropenia resolved except in one patient. 2 episodes of febrile neutropenia lead to permanent discontinuation of Exjade. The majority (95%) were manageable by medical/non medical treatment according to the MAH.

However, the review of this issue by the MAH is not enough reliable as there are problems between the definition of events and terms used by the coding system for this same event: agranulocytosis/febrile neutropenia (knowing that neutropenia is defined as PNN < 1500 /mm³ and a severe neutropenia (<500/mm³) and an agranulocytosis is a severe febrile neutropenia (*see also comment in PSUR 14 on this issue*). The addition of the term "agranulocytosis" in EU SPC should be discussed by the MAH as the MAH used widely the term "febrile neutropenia" without clear definition. Also, no data on the mean or median PNN level (NADIR) is provided. It seems that there is a discrepancy between the nature of the effect and the severity/seriousness reported.

The underlying disease for all paediatric patients is mentioned in table 13.1 of appendix 2 for 264 patients (73%) : mainly "other neoplasm" (35.5%), followed by "other disease" (16%), ALL (11%), aplastic anemia (9%) and AML (6%). Based on these data, we do not know the exact underlying disease for around 80% of patients (289/363) : either not known or "other neoplasm" or "other disease"... The MAH claims that it is not uncommon to observe neutropenia in patients with haematological malignancies. However, the MAH has not given relevant information on the cases in their analysis to confirm this hypothesis. We can suppose that as 46.2% of children (143/309) received antineoplastic agents (this proportion raised 67.1% (96/143) if we take the population who had

experienced an adverse effect and as some children experienced several episodes of neutropenia (96 febrile neutropenia in 62 patients) the MAH hypothesis might be plausible.

However, due to the high percentage of febrile neutropenia reports in paediatric patients (62/363 ; 17%) in this observational study, and as peripheral blood cytopenia is an important potential risk in the RMP of Exjade and should be closely monitored in upcoming PSURs, and as uncertainties remains on the definition taken for neutropenia/febrile neutropenia/agranulocytosis and the above MAH hypothesis for causes of neutropenia occurrence, the rapporteur considers that a specific comprehensive safety review of this issue (with time to onset, medical history/underlying conditions, circumstances of occurrence, risk factors, action taken and therapy given...) should be performed for paediatric patients enrolled in this study, especially to put into perspective with the underlying conditions of these paediatric patients. Indeed, a large proportion of patients had "other disease" but we do not know what sort of disease it concerns). A tabular format could be used and cases narratives with details on the PNN level for each case should be provided. In this review, the MAH should discuss the discrepancy observed between the nature of the effect and the severity/seriousness reported.

According to this comprehensive safety review conclusions, the MAH should also discuss the need to update the EU SPC (and RMP) considering the overall data on this issue available based on other clinical trials, spontaneous reporting and literature data.

Long term effects

Of note, a total of 263/363 (72.5%) received Exjade during less than 6 months. Among the 100 patients receiving Exjade more than 6 months (27.5%), only 32 (32%) received Exjade during more than 1 year. A total of 33 patients (67 AEs) were reported to having at least one AE among the 100 patients receiving more than 6 months of Exjade (33%). Similarly, 8 subjects experienced at least one AE among the 32 patients receiving more than 1 year of Exjade (25%). However, we don't know the type of effects occurring after 6 months of treatment.

As the long term safety in paediatric population (especially in youngest patients: 2-6 years-old) is listed as missing information in RMP of Exjade, we consider that the MAH should provide a more detailed safety analysis of paediatric patients enrolled in this study receiving Exjade for more than 6 months (with time to onset, medical history/underlying conditions, circumstances of occurrence, risk factors, action taken and therapy given...).

Of note, the study planned to present incidence of AEs by factors (including age) or AEs in special population. The objectives now is partially achieved as AEs were analysed for paediatric population but the MAH has not performed a sub-analysis by age categories. As this study contains the largest population of children (n=209 with children aged between 2 and <12 years-old) observed in real life conditions the MAH provided a sub-analysis of patients <u>by age category</u>: 2-6 years old , 7-12 years-old and 13- < 18 years old .

Similarly, a sub-analysis depending of transfusion status of paediatric patients should be done. Also, the MAH presented safety data depending of the dose of Exjade however, it would be more relevant to use dose unit in mg/kg/day (instead of mg/day) to interpret the data. All these 3 subanalysis should be performed.

As a <u>general comment</u>, a clear improvement of the data quality in upcoming documentation is awaited to allow accurate assessment of reliable data. Quality check should be performed carefully by the MAH to avoid discrepancies in term of numbers of events/cases, identification of duplicates (which should be taken into account in review). Issue partially addressed.

Question 3

Also, the MAH should commit to:

□ comply with the EMA guideline in terms of submission dates for future studies including paediatric data

□ consider to present paediatric data (efficacy and safety) separately for each future studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended.

MAH's Response

Article 46 of Regulation (EC) No 1901/2006 requires that any marketing authorization holder sponsored study which involves the use in the paediatric population of a medicinal product covered by a marketing authorization in EU, whether or not they are conducted in compliance with an agreed paediatric investigation plan, is to be submitted to the competent authority.

Following a recent inspection finding regarding late reporting of Non-Interventional Studies which include paediatric patients, Novartis has prepared a remediation plan to ensure that paediatric data is submitted in accordance with Article 46 of the Paediatric Regulation.

For future submissions, Novartis is committed to make all efforts:

 \Box to submit the final study report within six months of completion of the studies, which include paediatric patients treated with deferasirox and

 \Box to separately present the efficacy and safety data from paediatric patients treated with deferasirox, in all cases where sufficient data are available in paediatric patients.

CHMP's comment

The MAH's commitments are endorsed. Issue addressed.

Recommendation

Not fulfilled:

As a <u>general comment</u>, a clear improvement of the data quality in upcoming documentation is awaited to allow accurate assessment of reliable data. Quality check should be performed carefully by the MAH to avoid discrepancies in term of numbers of events/cases, identification of duplicates (which should be taken into account in review).

In their responses' document, the MAH committed to make all efforts:

- to submit the final study report within six months of completion of the studies, which include paediatric patients treated with deferasirox and
- to separately present the efficacy and safety data from paediatric patients treated with deferasirox, in all cases where sufficient data are available in paediatric patients.

which is acceptable for the rapporteur.

Efficacy data requested for study CICL670ATW01

As requested, the MAH provided a subgroup analysis to assess the relationship between ferritin level baseline and Exjade dose in the pediatric population. However, activity of deferasirox remains unclear in patients who had SF <1000 μ g/l at baseline. The MAH suggest that a dose increase of deferasirox may be needed to maintain SF below a recommended level of <1000 μ g/l. The design of this study could not allow to draw firm conclusions about the interest of a deferasirox treatment and/or the dose needed in this study population. However, new efficacy data in children aged 2 to less than 6 years at enrollment with transfusional hemosiderosis treated with deferasirox will be assessed in the frame of the variation II-48.

Safety data requested for study CICL670AKR01

The overall safety profile seems to be consistent with the known safety profile of Exjade and complications of underlying conditions in this study. However, we consider that additional analysis should be performed by the MAH to accurately assess the data from paediatric population as this study contains the largest population of children (n=209 with children aged between 2 and <12 years-old) observed in real life conditions (see section IV "Additional clarifications requested").

Additional clarifications requested

Safety data requested for study CICL670AKR01

1- Febrile neutropenia

- Due to the high percentage of febrile neutropenia reports in paediatric patients (62/363 ; 17%) in this observational study,
- as peripheral blood cytopenia is an important potential risk in the RMP of Exjade and should be closely monitored in upcoming PSURs,
- and as uncertainties remains
 - o on the definition taken for neutropenia/febrile neutropenia/agranulocytosis
 - o and the above MAH hypothesis for causes of neutropenia occurrence,

the rapporteur considers that a specific comprehensive safety review of this issue (with time to onset, medical history/underlying conditions, circumstances of occurrence, risk factors, action taken and therapy given...) should be performed for paediatric patients enrolled in this study, especially to put into perspective with the underlying conditions of these paediatric patients.

Indeed, a large proportion of patients had "other disease" but we do not know what sort of disease it concerns). A tabular format could be used and cases narratives with details on the PNN level for each case should be provided. In this review, the MAH should discuss the discrepancy observed between the nature of the effect and the severity/seriousness reported.

According to this comprehensive safety review conclusions, the MAH should also discuss the need to update the EU SPC (and RMP) considering the overall data on this issue available based on other clinical trials, spontaneous reporting and literature data.

2- Long term effects

As the long term safety in paediatric population (especially in youngest patients: 2-6 years-old) is listed as missing information in RMP of Exjade, we consider that the MAH should provide a more detailed safety analysis of paediatric patients enrolled in this study CICL670AKR01 receiving Exjade for more than 6 months (with time to onset, medical history/underlying conditions, circumstances of occurrence, risk factors, action taken and therapy given...).

3- Additional analysis (by age categories, by transfusion status and by dose (in mg/kg/day))

The study CICL670AKR01 planned to present incidence of AEs by factors (including age) or AEs in special population. The objectives now is partially achieved as AEs were analysed for paediatric population but the MAH has not performed 3 sub-analysis :

- One sub-analysis by age categories: 2-6 years old , 7-12 years-old and 13- < 18 years old .
- One sub-analysis by transfusion status
- One sub-analysis by dose (in mg/kg/day)

These 3 sub-analysis should be performed by the MAH.

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

MAH's responses (submitted in June 2016)

Question 1

Due to the high percentage of febrile neutropenia reports in paediatric patients (62/363; 17%) in this observational study,

- as peripheral blood cytopenia is an important potential risk in the risk management plan (RMP) of Exjade and should be closely monitored in upcoming periodic safety update reports (PSURs),
- and as uncertainties remain
 - on the definition taken for neutropenia/febrile neutropenia/agranulocytosis
 - and the above marketing authorization holder (MAH) hypothesis for causes of neutropenia occurrence,

the rapporteur considers that a specific comprehensive safety review of this issue (with time to onset, medical history/underlying conditions, circumstances of occurrence, risk factors, action taken and therapy given...) should be performed for paediatric patients enrolled in this study, especially to put into perspective with the underlying conditions of these paediatric patients.

Indeed, a large proportion of patients had "other disease" but we do not know what sort of disease it concerns). A tabular format could be used and cases narratives with details on the PNN level for each case should be provided. In this review, the MAH should discuss the discrepancy observed between the nature of the effect and the severity/seriousness reported. According to this comprehensive safety review conclusions, the MAH should also discuss the need to update the EU Summary of Product Characteristics (SmPC) (and RMP) considering the overall data on this issue available based on other clinical trials, spontaneous reporting and literature data.

Summary of MAH's response

Although febrile neutropenia was a common adverse event (AE) observed in this trial (62/363; 17%), a large confounder factor was observed in 100% of these subjects; all subjects with febrile neutropenia had a pre-existing neoplasms/cancer condition in association with antineoplastic, cytotoxic treatment.

, , , ,								
	2 ≤ Age< 7		7 ≤ Age< 13		13 ≤ Age< 18		All patients	
	n	(%)	n	(%)	n	(%)	n	(%)
Yes	33	(100.00)	17	(100.00)	12	(100.00)	62	(100.00)
No	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)
Total	33	(53.23)	17	(27.42)	12	(19.35)	62	(100.00)
Neoplasm	33	(100.00)	17	(100.00)	12	(100.00)	62	(100.00)
Diseases of the blood and blood-forming organs and certain disorders	2	(6.06)	1	(5.88)	1	(8.33)	4	(6.45)
Endocrine, nutritional and metabolic disease	0	(0.00)	2	(11.76)	0	(0.00)	2	(3.23)
Certain infectious and parasitic diseases	0	(0.00)	0	(0.00)	1	(8.33)	1	(1.61)
Symptoms, signs and abnormal clinical and laboratory findings, NEC	1	(3.03)	1	(5.88)	1	(8.33)	3	(4.84)

Table 2-1Current medical conditions* of patients who had febrile neutropenia
by age categories

* Diseases classified according to Korean Standard Classification of Disease as described in the Data Management Plan

Table 2-3	Concomitant medication of patients who had febrile neutropenia by
	age categories

	2 ≤ Age< 7		7 ≤ A	.ge< 13	13 ≤ Age< 18		All patients	
	n	(%)	n	(%)	n	(%)	n	(%)
Yes	33	(100.00)	17	(100.00)	12	(100.00)	62	(100.00)
No	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)
Total*	33	(53.23)	17	(27.42)	12	(19.35)	62	(100.00)
	1							
ANTINEOPLASTIC AGENTS	31	(93.94)	15	(88.24)	11	(91.67)	57	(91.94)
Cytotoxic agent	31	(93.94)	15	(88.24)	11	(91.67)	57	(91.94)

Patients with febrile neutropenia received a mean frequency of 10.28 (\pm 4.21) transfusions with a range between 3 to 20. The mean period of transfusion was 0.74 years (\pm 1.09) with a range of 0.10 to 8 years. All patients with documented blood transfusion and febrile neutropenia received less than 7 ml/kg/month of packed red blood cells (see Table 2-4). This is consistent with the assumption

that most of the children required blood transfusion in context of their underlying malignant disease and/or antineoplastic treatment.

Deferasirox treatment was permanently discontinued in six subjects (3.59% of the cases). In 17 cases (10.18%), no actions were taken following the occurrence of febrile neutropenia

All but one patient recovered from the condition of febrile neutropenia (see Table 2-6). For all cases, relationship to study drug was assessed as unlikely (not suspected)

Cases narratives with details on the polymorphonuclear neutrophil counts (PNN) level for each case cannot be provided, as the case report form (CRF) of study ICL670AKR01 did not mandate collection of this information.

In study CICL670A2301 'International sentinel site surveillance of patients with transfusional hemosiderosis treated with Exjade (deferasirox) in actual practice setting' recently submitted in the context of the type II variation (II-50), febrile neutropenia was not reported in any of the 66 pediatric patient aged less than 18 years during the 3-year-observation period. Pediatric patients enrolled in the study had the following underlying hematologic diseases: β - thalassemia major (34 patients, 49.3%); β -thalassemia intermedia (7 patients, 10.1%); sickle cell (24 patients, 34.8%); diamond-blackfan anemia (2 patients, 2.9%) and other (2 patients, 2.9%).

The SmPC adequately describes the reports of cytopenias, leukopenias and aggravation of these cytopenias (section 4.4 Warning and Precautions)

In conclusion, the event of febrile neutropenia is not unexpected in this patient population with neoplasms and treated with cytotoxic agents, as those are important confounding factors known to increase risk for febrile neutropenia. The current SmPC and RMP adequately describe the risk of peripheral blood cytopenias, leukopenias and aggravation of these cytopenias and no changes to the SmPC and RMP are warranted based on these data.

CHMP's comment

The safety review provided shows that all pediatric patients presenting febrile neutropenia had a preexisting neoplasms/cancer condition and were treated with antineoplastic, cytotoxic treatment causing neutropenia. The need for frequent transfusion in this population was the consequence of the severity of their malignant disease and the use of cytotoxic agents. It remains that the narratives of the cases have not been provided, and the numerous tables provided do not allow to have a clear view of the medical history and risk factors for neutropenia.

On the other hand, it is acknowledged that neutropenia in relation to the treatment was rarely observed in study CICL670A2301 'International sentinel site surveillance of patients with transfusional hemosiderosis treated with Exjade (deferasirox) in actual practice setting' recently submitted in the context of the type II variation (II-50), and no severe febrile neutropenia was reported in any of the 66 pediatric patient aged less than 18 years during the 3-year-observation period. Of note, the underlying hematologic diseases for the pediatric patients enrolled in the study were β -thalassemia and sickle cell and diamond-blackfan anemia.

In conclusion, even though the febrile neutropenia are likely to be driven by the underlying malignant diseases in these pediatric patients, the paucity of the description of these cases cannot allow to exclude a role of deferasirox in the aggravation of neutropenia leading to severe neutropenia.

The current wording in the SPC is considered appropriate as soon as the role of deferasirox in cytopenia is more precisely described.

Point solved

Question 2

Long term effects

As the long term safety in paediatric population (especially in youngest patients: 2-6 yearsold) is listed as missing information in RMP of Exjade, we consider that the MAH should provide a more detailed safety analysis of paediatric patients enrolled in this study CICL670AKR01 receiving Exjade for more than 6 months (with time to onset, medical history/underlying conditions, circumstances of occurrence, risk factors, action taken and therapy given...).

Summary of MAH's response

Out of the 363 paediatric patients, 100 patients (27.55%) were treated for longer than 24 weeks; slightly less patients in the youngest age category (24.79%) and more patients in the oldest age category (29.13%). The mean period of Exjade treatment in the 100 pediatric patients who received deferasirox for longer than 24 weeks was 299.32 (\pm 140.70) days. More patients in the middle age category were treated for a period between 9 to less than 12 months (24.24%) and for longer than 12 months (36.36%) compared to in the youngest (20% and 30%, respectively) and in the oldest category (18.92% and 29.73%, respectively).

Out of 100 paediatric patients receiving deferasirox for longer than 24 months, 60 patients had a documented current medical condition. Thirty patients (50.00%) had diseases of the blood and blood forming organs and certain disorders and 28 patients (46.67%) had a neoplasm.

Forty-six patients (62.16%) who received deferasirox for longer than 24 months, were also treated with systemic anti-infectives (see Table 2-10), similarly to the overall pediatric population where 64.40% received anti-infectives (see Table 14 of Appendix 2 of first response to question). Less patients, who were treated with deferasirox for longer than 24 months, received cytotoxic agents (37.84%) and hematopoeitics (growth factors) (29.73%) compared to the overall pediatric population (45.63% and 37.54%, respectively).

Medical/non-medical treatment was administered in 42 cases (62.69%). In 15 cases (22.39%), no actions were taken following occurrence of AE (see Table 2-11). More cases in the middle age group (33.33%) had dose modification or temporary discontinuation compared to the youngest (0.00%) and oldest age category (3.23%). Deferasirox treatment was permanently discontinued in none of the patients treated for longer than 6 months indicating that these patients can remain on deferasirox treatment with adequate monitoring.

In the 100 patients treated for longer than 6 months, deferasirox treatment was never permanently discontinued indicating that these patients can remain on deferasirox treatment with adequate monitoring.

CHMP's comment

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006 EMA/CHMP/763315/2016

Treatment conditions, medical conditions, concomitant medications and AE-driven treatment adaptations have been analysed according to age categories.

Question 3

Additional analysis (by age categories, by transfusion status and by dose (in mg/kg/day))

The study CICL670AKR01 planned to present incidence of AEs by factors (including age) or AEs in special population. The objectives now is partially achieved as AEs were analysed for paediatric population but the MAH has not performed 3 sub-analysis :

- One sub-analysis by age categories: 2-6 years old , 7-12 years-old and 13- < 18 years old
- One sub-analysis by transfusion status
- One sub-analysis by dose (in mg/kg/day)

These 3 sub-analysis should be performed by the MAH.

Summary of MAH's response (see MAH response document for more details in Tables)

Detailed safety analyses by age categories, transfusion status and daily dose are presented as follows:

- Serious adverse event (SAE)/ serious adverse drug reaction (SADR)
- Unexpected AE/adverse drug reaction (ADR)
- AE/ADR
- Details of AE by severity
- Details of AE by outcome
- Details of AE by causality

Analyses by age categories

The mean age of pediatric patients was 9.51 (\pm 4.7 years) with a range between 2 to 17 years.

Analyses were performed for all 363 pediatric patients by age categories:

2 ≤ Age < 7 7 ≤ Age < 13 13 ≤ Age < 18

Paediatric patients were evenly distributed across the 3 age categories with 33.3%, 31.7% and 34.99% for the youngest, middle and oldest category respectively. Overall more males (62.26%) than females (37.74%) were enrolled. The majority of the pediatric patients were diagnosed with oncologic conditions such as other neoplasms (35.54%), acute lymphocytic leukemia (10.74%), aplastic anaemia (9.37%) and acute myeloid leukemia (6.34%). Treatment discontinuations were similar in pediatric patients across age groups with less than half stopping chelation (41.87%). Adverse event was cited as reason for Exjade discontinuation in 28.95% of the cases. There were relatively more discontinuations due to AE (38.78%) in the oldest age category. In the younger age categories, there were more discontinuations due to improvement (15.69% in the youngest and 15.38% in the middle age category).

There were less reports of SAE (3.31%) in the youngest age category compared to the middle (6.09%) and oldest (5.51%) age groups. The incidence of unexpected AE is higher in the youngest age group (35.54%) than in the middle (26.09%) and oldest age group (24.41%). Unexpected ADR, AE and ADR were more frequent in the oldest age group compared the youngest age groups. Incidence of mild AE was slightly higher in the youngest (73.17%) and oldest (71.43%) age group compared to the middle age group (67.24%). Frequency of moderate AEs were comparable across age groups. There were more reports of severe AE in the middle age group. In all age groups, the vast majority of the AE were considered recovered (overall: 91.40%) or under recovery (overall 4.57%). In few cases, the patients did not recover from the AE and the frequencies were comparable across age groups (overall 2.96%).

In the middle age group, 3 patients experienced fatal AEs (3.45%) and none in the youngest and oldest age groups. None of the deaths was suspected to be related to deferasirox: 1 case of septic shock, 1 case of disease progression, 1 case of encephalopathy and same case of disease progression.

The causality was assessed as 'unlikely' for the majority of the AEs in all age groups (overall 75.27%, more frequently in the youngest age group) and possible in 18.28% of the cases. In the oldest age group, there were more AE which were assessed as 'possible' compared to the youngest age groups. Rarely, the causality was assessed as 'likely', slightly more frequently in the youngest age and oldest age groups (4.88% and 3.76%) than in the middle age group (1.72%) In the oldest age group, the causality for the AE of rash was assessed as certain

Analyses by transfusion status

There were 302 out of 363 pediatric patients who had documented transfusions with a mean frequency of 14.22 (\pm 13.69) and a range between 1 to 188. The mean period of transfusion was 1.77 years (\pm 2.15) with a range of 0.10 to 15 years. The majority of the patients (98.68%) received less than 7 ml/kg/month of packed red blood cells. No pediatric patients received blood transfusion >14 ml/kg/month. In the youngest and middle age groups, all children (100%) received less than 7 ml/kg/month and 96.23% (n=102) in the group of oldest pediatric patients. In the oldest age category, 4 patients (3.77%) received more than 7 ml/kg/month but less than 14 ml/kg/month of packed red blood cells.

Nearly all patients (98.68%) were in the transfusion group of less than 7 ml/kg/month. No patient in the other transfusion categories experienced an SAE, SADR, unexpected AE or unexpected ADR. In the transfusion group of \geq 7 to \leq 14 ml/kg/month, one AE and one ADR were reported.

In the transfusion group of <7 ml/kg/month, there were more reports of mild (67.17%) than moderate (30.70%) and severe (2.13%) AEs. In the transfusion group \geq 7 to \leq 14 ml/kg/month, the single AE that was reported was considered as mild.

In the transfusion group <7 ml/kg/month, the majority of the patients recovered from the AE (91.79%); in 11 cases (3.34%), the patients did not recover from the AE. The 4 fatal cases described above were in the transfusion group <7 ml/kg/month. In the transfusion group \geq 7 to \leq 14 ml/kg/month, the single AE was considered recovered.

In the transfusion group <7 ml/kg/month, the causality was assessed as 'unlikely'for the majority of the AEs (75.76%). In the transfusion group \geq 7 to \leq 14 ml/kg/month, the causality for the AE of rash was assessed as 'certain' (see Table 25.2.2 of Appendix 1) and the severity of the rash event was 'mild' (see Table 22.2.2 of Appendix 1).

Analyses by dose

Mean daily doses of deferasirox were similar between the three age categories with confidence interval widely overlapping between the groups. Patients in the youngest age category received a slightly higher median dose $(21.63 \pm 5.91 \text{ mg/kg/d})$ compared to pediatric patients in the middle and oldest age category (18.9 ± 5.39 and 18.65 ± 5.47 mg/kg/d respectively). In the youngest age category, 6 patients (4.96%) received daily doses higher than 30 mg/kg/d, 2 patients (1.75%) in the middle age category and 3 patients (2.36%) in the oldest age category.

In the youngest age group, 35.54% of patients received DFX dose of 10 to <20 mg/kg/d while 58.68% received 20 to <30 mg/kg/d. Only 1 patient (0.83%) received doses lower than 10mg/kg/d. In the middle and oldest age group, more than half of the patients were treated with doses of 10 to <20 mg/kg/d (54.39% and 55.12%, respectively) and approximately one third (37.72% and 36.22%, respectively) received doses between 20 to <30 mg/kg/d. In these groups more patients received doses below 10 mg/kg/d (6.14% and 6.30%).

Few patients were treated with doses <10 and \geq 30 mg/kg/day compared to the other groups. In the groups of 10 to <20 and 20 to <30 mg/kg/day, the incidence of SAE was comparable (5.71 and 5.00%, respectively). There were more report of AEs and unexpected AEs in the group of 20 to <30 mg/kg/day (54.38 and 38.13%) compared to the group of 10 to <20 mg/kg/day (44.57 and 27.71%).

The majority of the AE were reported as mild (70.70%) except for the group of \geq 30 mg/kg/day in which 2 events (66.67%) were moderate. In the lowest dose group, there were slightly more mild AE report, which is consistent with known safety profile of defension.

In all dose groups, the majority of the patients recovered from the AE (91.40%). In the group 20 to <30 mg/kg/day more patients (3.88%) did not recover from the AE compared to the group 10 to <20 mg/kg/day. The 4 fatal cases described above were all in the group of patients receiving deferasirox at a dose between 10 to <20 mg/kg/day.

The causality was assessed as 'unlikely' for the majority of the AEs in all dose groups (overall 75.27%) and more frequently in the group of 20 to < 30 mg/kg/day. In the group < 10 mg/kg/day, there were more AE which were assessed as 'possible' compared to other dose groups. Rarely, the causality was assessed as 'likely' (3.49% overall), with highest frequency in the lowest and highest dose group probably due to the low number of patients in these groups.

<u>Summary</u>

The MAH concluded that the additional safety analyses performed for the 363 pediatric patients by age, transfusion and dose categories are consistent with the known safety profile of deferasirox and no new safety signals were identified.

Pediatric patients were evenly distributed across the 3 age categories. Overall more males than females were enrolled consistently with data in pediatric malignancies in Korea. Nearly all patients received less than 7 ml/kg/month of packed red blood cells.

Few patients were treated with doses <10 and \geq 30 mg/kg/day compared to the other groups. There were more report of AE and unexpected AEs in the group of 20 to <30 mg/kg/day compared to the group of 10 to <20 mg/kg/day and in both groups the incidence of SAE was comparable.

There were more discontinuations due to AE in the oldest age category. In the youngest age categories, there were more discontinuations due to improvement. This observation of efficacy is in

line with the transfusional iron burden and daily dose described below. More patients in the youngest age category (58.68%) were treated with a higher daily dose of 20 to <30 mg/kg/day of deferasirox, while they received less than 7 ml/kg/month of packed red blood cells. These data may suggest that a shorter duration of deferasirox treatment may be associated with efficacy especially in children of the youngest age category who were tolerant to higher doses of deferasirox.

In the youngest age category, there were less reports of SAE and more unexpected AE compared to the middle and oldest age groups. Unexpected ADR, AE and ADR were more frequent in the oldest age group compared the youngest age groups. There were more reports of severe AE in the middle age group. In the transfusion group \geq 7 to \leq 14 ml/kg/month and oldest age group, the causality for one mild AE of rash was assessed as 'certain' in one patient receiving a daily dose between 20 to < 30 mg/kg of deferasirox.

In all age and dose groups, the vast majority of the AE were considered recovered. In the middle age group, 3 patients, all treated with a deferasirox dose between 10 to <20 mg/kg/day, experienced 4 fatal AE. None of the deaths was suspected to be related to deferasirox.

The causality was assessed as 'unlikely' for the majority of the AEs in all age groups and all dose groups, with a higher frequency in the youngest age group and in the dose group of 20 to <30 mg/kg/day. In the oldest age category and in the group <10 mg/kg/day, there were more AEs which were assessed as 'possible' than in the other age and dose groups. Rarely, the causality was assessed as 'likely' (3.49% overall), more frequently in the youngest age and oldest age groups as well as in the group of 30 mg/kg/day.

The MAH concluded that the results obtained from the additional analyses performed in the pediatric patients from study CICL670AKR01 are consistent with the associated risks of the underlying disease of this patient population and the known safety profile of deferasirox in pediatric and adult patients.

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 pediatric information of the current Exjade (deferasirox) Core Data Sheet and RMP 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 SmPC and RMP.

CHMP's comment

Overall, the conclusion drawn by the MAH are endorsed.

A detailed analysis has been performed with 3 sub-analysis by age categories, transfusion status and dose. Some differences in (serious) adverse drug reaction and (serious) adverse event, have been observed between age categories.

The analysis by transfusion status is poorly informative as all but 4 patients received less than 7 ml/kg/month.

Some difference of exposure to deferasirox were observed between age category as the patients in the youngest category were more frequently exposed to 20-30 mg/kg/day than the patients in the oldest category who received more frequently 10-20 mg/kg/day. This difference reflects the capacity of young patients to tolerate higher dose, leading to a shorter exposure.

There is no safety signal emerging from this analysis, nor any new safety information of interest to be added in the core data sheet.

These data are also in line with the assessment of the study A2411 which has been positively assessed in the frame of the Procedure No. EMEA/H/C/000670/II/0048, and where the long-term safety of deferasirox for children aged 2 to less than 6 years at enrolment with transfusional hemosiderosis.

Recommendation

Fulfilled: