15 November 2012
EMA/44672/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Exjade (deferasirox)

Procedure No. EMEA/H/C/000670/II/0026

Note

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

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List of abbreviations

ANCOVA	Analysis of covariance
AE	Adverse event
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
Dw	Dry weight
FAS	Full analysis set
Hb	Haemoglobin
HbE	Haemoglobin E
HbH	Haemoglobin H
HH	Hereditary hemochromatosis
LFT	Liver function test
LIC	Liver iron concentration
NTBI	Non-transferrin-bound serum iron
NTDT	Non-transfusion-dependent thalassemia
MRI	Magnetic resonance imaging
SAE	Serious adverse event
SD	Standard deviation
SF	Serum ferritin
SOC	System organ class
SSC	Study Steering Committee
ULN	Upper limit of normal
UMI	Unconditional mean imputation
UPCR	Urine protein/creatinine ratio

1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd. submitted to the European Medicines Agency on 8 December 2011 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	International non-proprietary name:	Presentations:
Exjade	deferasirox	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH proposed a new indication of Exjade for the treatment of chronic iron overload requiring chelation therapy in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older. Consequently, changes are proposed to sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC and the package leaflet.

The requested variation proposed amendments to the SmPC and Package Leaflet.

Exjade was designated as an orphan medicinal product EU/3/02/092 on 13 March 2002. Exjade was designated as an orphan medicinal product in the following indication: treatment of chronic iron overload requiring chelation therapy.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0216/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0216/2011 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 26 June 2008. The Protocol Assistance pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment

Rapporteur: Pierre Demolis Co-Rapporteur: Luca Pani

Submission date:	8 December 2011
Start of procedure:	18 December 2011
Rapporteur's preliminary assessment report circulated on:	10 February 2012
Rapporteur's updated assessment report circulated on:	13 February 2012
Co-Rapporteur's assessment report circulated on:	29 February 2012
Rapporteur's & Co-Rapporteur's joint assessment report circulated on:	09 March 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	15 March 2012
MAH's responses submitted to the CHMP on:	20 April 2012
Rapporteur's joint assessment report on the MAH's responses circulated on:	5 June 2012
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	21 June 2012
MAH's responses submitted to the CHMP on:	16 August 2012
Rapporteur's joint assessment report on the MAH's responses circulated on:	9 October 2012
3rd Request for supplementary information and extension of timetable adopted by the CHMP on:	18 October 2012
MAH's responses submitted to the CHMP on:	25 October 2012
Rapporteur's joint assessment report on the MAH's responses circulated on:	02 November 2012
CHMP opinion:	15 November 2012

2. Scientific discussion

2.1. Introduction

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

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

- in patients with beta thalassaemia major with iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) aged 2 to 5 years,
- in 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 patients with other anaemias aged 2 years and older.

Chronic iron overload may result from repeated transfusions (transfusional hemosiderosis) or from an increased intestinal absorption of iron, which is the primary source of iron overload in such conditions as hereditary hemochromatosis (HH) and non-transfusion dependent thalassemia (NTDT). Chronic iron overload, if left untreated, often results in serious complications such as liver abnormalities as well as cardiac, metabolic and endocrine disturbances. The goals of iron chelation therapy are to remove the amount of iron administered in blood transfusions or through intestinal overabsorption and, as required, to reduce the existing iron burden.

Thalassaemic disorders are a heterogeneous group of congenital blood disorders characterized by a partly or completely suppressed production of normal haemoglobin due to impaired synthesis of haemoglobin subunits, namely α-globin and β-globin.

The clinical picture of thalassemia may be mild (thalassemia minor), moderate (NTDT) or severe (thalassemia major). Patients with thalassemia minor are asymptomatic, while patients with thalassemia major present with severe anaemia early in life requiring regular blood transfusions and chelation therapy to prevent or reverse transfusional iron overload. Patients with non-transfusion dependent thalassemia (e.g., β-thalassemia intermedia, HbE β-thalassemia, and HbH α-thalassemia) have milder anaemia compared to thalassemia major and therefore they require no or only occasional blood transfusions. Despite that, NTDT patients develop clinically relevant iron overload, mainly due to an increased intestinal absorption of iron driven by anaemia due to ineffective erythropoiesis.

The mechanism of iron loading in NTDT is considered similar to that described for HH in that it is a direct result of down-regulation of hepcidin, leading to increased gastro-intestinal absorption of iron. In HH the low hepcidin levels are related to a mutation in the HFE gene while in NTDT, the low hepcidin levels are a compensatory response to the anaemia.

In this application, the MAH proposed a new indication of Exjade for the treatment of chronic iron overload requiring chelation therapy in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.

This proposed new indication for deferasirox is based on a randomized, placebo-controlled phase II Study CICL760A2209 and Study A2202/E Study CICL670A2202/E, a phase I/II open-label, dose escalation study in HH patients, provides additional safety data.

2.2. Non-clinical aspects

In this application, the MAH assumed that the prevalence of non-transfusion-dependent thalassemia patients with clinically significant iron overload is assumed to be in the same range as the prevalence of transfusion-dependent thalassemia intermedia (which represents 2 - 14% of the total number of transfusion-dependent thalassemia patients). As a consequence, it was not expected to lead to any significant increase in the environmental exposure to deferasirox drug substance for the following reasons:

(1) in Europe, iron-overloaded patients with non-transfusion-dependent thalassemia (NTDT) syndromes constitute a small minority of patients with chronic iron overload requiring chelation therapy;

(2) unlike in transfusional iron overload, where life-long, continuous chelation therapy is required, treatment of NTDT patients will be intermittent and is estimated to be needed during less than 10% of a patient's lifetime. The number of patients on treatment at any one time is expected to reflect this ratio;

(3) because of the absence of ongoing transfusional iron intake, a lower maximum dose will be recommended in these patients (20 mg/kg/day, as opposed to 40 mg/kg/day in transfusional haemosiderosis).

Furthermore, the ERA submitted at the time on initial marketing authorisation was based on a conservative approach for the calculation of the potential environmental exposure.

Therefore, this new indication is not expected to adversely affect the initial environmental risk assessment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Purpose	Number of patients enrolled	Details	Status
Pivotal study	166 in core 133 in extension	**Study A2209**: A randomized, double-blind, placebo-controlled, phase II study to evaluate efficacy and safety of deferasirox in non-transfusion-dependent thalassemia patients with iron overload	Completed (core) Ongoing (extension)
Supportive study	49 in core 26 in extension	**Study A2202/E**: A phase I/II open-label, dose escalation trial to explore the safety and efficacy of ICL670 in patients with iron overload resulting from hereditary hemochromatosis	Completed (core + extension)

Source: [Study A2209], [Study A2202/E]

2.3.2. Pharmacokinetics

Study CICL670A2202 was a Phase I/II open-label, dose-escalation trial to evaluate the safety and efficacy of deferasirox in patients with iron overload resulting from hereditary haemochromatosis (HH).

Pharmacokinetic blood sampling were performed only at the week 4, 8, 12, 16, 20 and last visit (week 24) in the core phase. The pharmacokinetic blood sampling was performed just prior to administration of the next deferasirox dose or approximately 24 hours after the previous dose (pre-dose trough value). This visit was scheduled in the morning, in order to allow patients to withhold deferasirox.

All subjects with evaluable PK parameters were to be included in the data analysis. The relationship between drug concentration and the pharmacodynamic variable were to be examined by fitting PK model, (type of model, software, statistical tests).

Summary statistics of deferasirox trough concentrations is provided in Table 1.

Table 1 – Descriptive statistics for deferasirox trough concentrations [umol/L], by dose cohort (Per-protocol population)

	5 mg/kg/day N=11	10 mg/kg/day N=15	15 mg/kg/day N=22
Week 4			
N	10	14	17
Mean (SD)	9.63 (8.783)	19.62 (9.502)	30.48 (20.201)
Median	6.70	18.90	25.90
Range	1.0 - 31.5	0.0 - 34.2	0.0 - 61.3
Week 8			
N	10	12	17
Mean (SD)	8.86 (5.828)	23.88 (22.787)	27.06 (21.686)
Median	7.91	17.45	16.50
Range	2.1 - 23.5	0.0 - 86.6	0.0 - 73.1
Week 12			
N	10	12	13
Mean (SD)	10.58 (11.752)	28.71 (23.849)	23.39 (11.403)
Median	6.40	24.00	23.70
Range	3.2 - 42.6	2.7 - 92.2	0.0 - 44.1
Week 16			
N	10	11	11
Mean (SD)	12.38 (11.634)	21.62 (16.539)	21.80 (18.713)
Median	8.83	15.30	16.30
Range	4.3 - 43.5	0.0 - 51.6	0.0 - 56.6
Week 20			
N	9	10	8
Mean (SD)	11.72 (10.316)	26.47 (17.934)	27.58 (25.324)
Median	9.14	22.40	18.90
Range	4.1 - 38.2	9.3 - 66.1	6.9 - 86.5
Week 24			
N	10	9	6
Mean (SD)	14.62 (12.216)	21.32 (21.840)	26.83 (11.178)
Median	10.70	15.00	27.95
Range	1.0 - 40.7	0.0 - 64.3	7.7 - 40.2

Source: PT-Table 14.2-2.4

2.3.3. Discussion and conclusions on clinical pharmacology

Steady-state pharmacokinetics of deferasirox was achieved by week 4 for 5, 10, and 15 mg/kg. Mean trough concentrations at week 4 were approximately dose proportional.

This is only true for week 4. Indeed, concentrations corresponding to 10 and 15 mg/kg/day from Week 8 appear similar (the expected ration was not observed). That may explain that the overall efficacy in the 15 mg/kg/day group was not statistically better than in the 10 mg/kg/day group.

Difference in deferasirox plasma exposure between HH or NTDT versus patients with transfusion-dependent iron overload (i.e., higher exposure in patients with HH or NTDT) and difference in Deferasirox plasma exposure between healthy subjects versus patients with transfusion-dependent iron overload (i.e., higher exposure in healthy subjects) are consistent: greater exposure due to the fact “that chelatable iron levels are much lower in healthy patients” or both HH or NTDT patients than in patients with transfusion-dependent iron overload.

Therefore, the lower recommended initial daily dose of Exjade in non-transfusion-dependent patients in comparison with transfusion-dependent patients is justified (10 and 20 mg/kg/day, respectively).

2.4. Clinical efficacy

2.4.1. Main study CICL670A2209 (THALASSA)

Methods

Study No CICL670A2209 (THALASSA) was a randomized, double-blind, placebo-controlled, phase II study to evaluate efficacy and safety of deferasirox in non-transfusion-dependent thalassemia patients with iron overload.

Study Participants

The main criteria for inclusion were: male or female patients ≥10 years of age (≥18 years in Greece only) with NTDT syndromes, who had not received any transfusion within the 6 months prior to entry into the study with LIC ≥ 5 mg Fe/g dw measured by R2 MRI and serum ferritin >300 ng/mL at screening (two consecutive values at least 14 days apart from each other).

Treatments

Two different deferasirox starting doses (5 and 10 mg/kg/day) were evaluated. The placebo control comprised matching dose. Patients received treatment for 52 weeks. Doubling of the randomization dose (up to 20 mg/kg/day) was considered after 24 weeks of treatment in patients without ≥15% decrease in LIC and with LIC ≥ 7 mg Fe/g dw. At end of study patients could enter a one-year extension study.

Any additional therapy aimed to treat non-transfusion dependent thalassemia during this trial (e.g. therapy with hydroxyurea, erythropoietin, butyrate) is not allowed. Except for the study medication, no other iron chelation therapy was administered while patients were enrolled in this trial.

Objectives

Primary objective:
To compare the efficacy of two regimens of deferasirox administration (starting doses of 5 and 10 mg/kg/day) in patients with non-transfusion-dependent thalassemia (NTDT) based on change in liver iron content (LIC) from baseline after one year of treatment compared to placebo treated patients.

Secondary objectives:

- To compare the efficacy of two regimens of deferasirox administration (starting doses of 5 and 10 mg/kg/day) based on change in LIC from baseline after 6 months of treatment with the placebo-treated patients
- To compare change in serum ferritin over one year of treatment between deferasirox and placebo
- To evaluate the safety of both regimens of deferasirox versus placebo in NTDT patients
- To evaluate efficacy and safety of dose doubling
- To evaluate the last LIC value under doubled dose to the last value of LIC before the doubling of the dose
- To evaluate the relationship between serum ferritin and LIC

- To assess the change from baseline in haematological and iron metabolism parameters (e.g. haemoglobin, transferrin saturation)
- To evaluate the iron accumulation rate based on LIC assessment in NTDT patients treated with placebo.

Outcomes/endpoints

Efficacy: The primary efficacy parameter was the change in LIC from baseline after 12 months of treatment with study drug. Change in LIC at 6 months was a secondary efficacy endpoint. Other secondary objectives were serum ferritin assessment, change from baseline in haematological and iron metabolism parameters and iron accumulation rate evaluation.

LIC was measured using a validated R2 MRI technique both at screening (Visit 1 or Visit 2), Month 6 (Visit 12), and EOS. All patients enrolled in the study had MRI scans using a specific sequence and raw image data was analysed centrally to determine the patient's LIC value.

Serum ferritin levels were measured at screening (Visit 1 and Visit 2) and then at Visit 7 and at every subsequent study visit (except Visits 121, 122 and 123) by a central laboratory.

Haematological and iron metabolism parameters: total serum iron, serum transferrin, transferring saturation, soluble transferrin receptor, non-transferrin-bound iron [NTBI], labile plasma iron [LPI], serum erythropoietin, reticulocyte count, nucleated red blood cell count [NRBC], haemoglobin, plasma haemoglobin, plasma haptoglobin, lactate dehydrogenase [LDH], plasma hepcidin and growth differentiation factor 15 (GDF15).

Safety: Safety was assessed by monitoring the frequency, duration and severity of adverse events (AEs), clinical evaluations (physical examinations, vital signs, body weight, auditory and ocular tests, echocardiography, ECG) throughout the study, as well as clinical laboratory analyses.

Sample size

The sample-size was determined to obtain 90% power for showing superiority of at least 1 deferasirox treatment group over placebo with respect to change from baseline in LIC at Week 52. A sample-size of 46 patients in each deferasirox group and 23 in each matching placebo group (138 patients in total) is sufficient to achieve 90% power to reject at least 1 of the 2 null hypotheses comparing deferasirox to placebo with the multiplicity adjustment described in study protocol.

Considering a potential of 10% patients without any post-baseline LIC value, the sample-size needed to be increased to 52 patients for each deferasirox group and to 26 for each placebo group (156 patients in total).

Randomisation

The randomization ratio was 2:1:2:1 (5 mg/kg/day deferasirox / matching placebo dose / 10 mg/kg/day deferasirox / matching placebo dose).

Blinding (masking)

This was a double-blind study (treatment was blinded, dose was not blinded), and patients, investigator staff, persons performing the assessments and data analysts remained blind to the identity of the treatment from the time of randomization until database lock.

Statistical methods

Primary efficacy analysis (Absolute change of LIC at Week 52)

The primary efficacy variable was the absolute change in LIC from baseline to Week 52, i.e. the difference of LIC at Week 52 minus LIC at baseline. If no LIC measurement was available at Week 52, the last available post-baseline LIC measurement before Week 52 was used. The study was to be claimed successful if the superiority of at least 1 deferasirox treatment group (starting dose of 5 or 10 mg/kg/day) relative to placebo could be demonstrated with regard to the primary efficacy endpoint. Multiplicity was addressed by statistical test procedures controlling a 1-sided family-wise type I error rate to 0.025 and 2-sided simultaneous 95% confidence intervals. Analysis of covariance (ANCOVA) was performed with 1-sided t-tests using Dunnett's adjustment for multiple comparisons to the placebo control group. In case both deferasirox groups were statistically superior to placebo (and only in this case), the 2 deferasirox groups were compared by means of a 2- sided t-test at a significance level of 5%.

Secondary efficacy analysis

Absolute Change from baseline LIC at Week 24 was analysed in the same way as the primary efficacy variable on the Full Analysis Set (FAS).

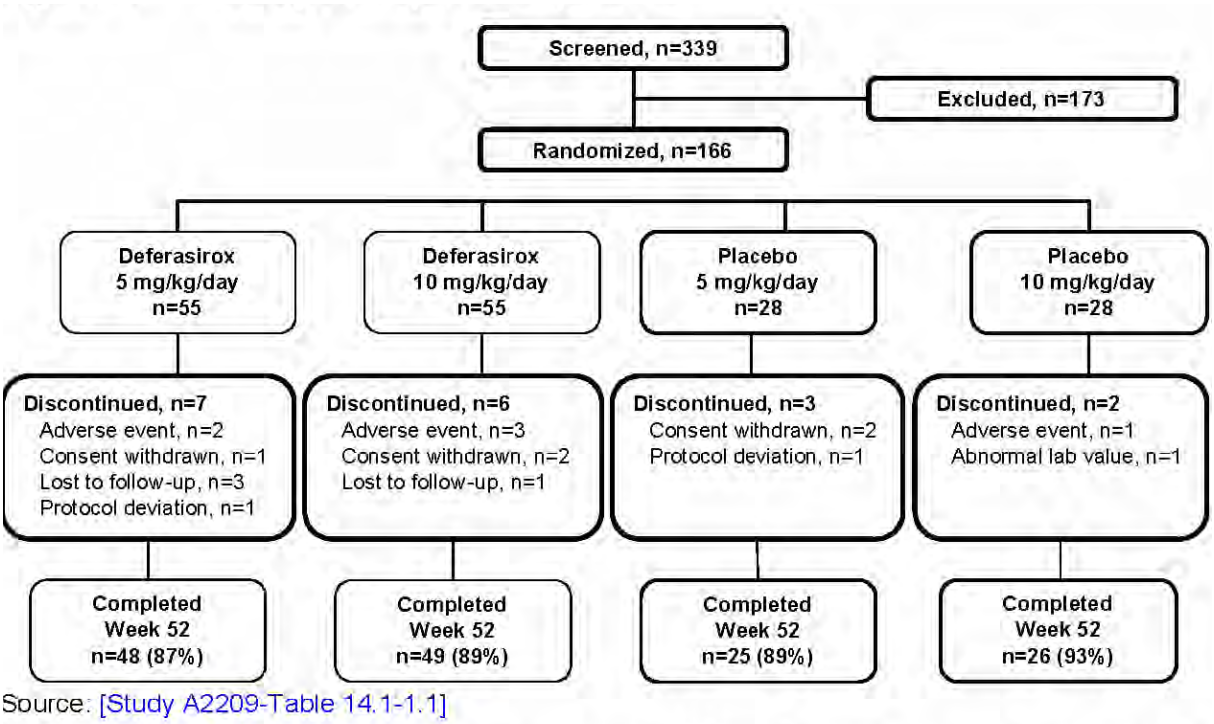
For serum ferritin quarterly change from baseline, a mixed effect model was fitted on the with-fixed factors treatment, quarter, and treatment-by-quarter interaction. An unstructured correlation matrix was assumed for measurements taken within the same patient. In the rare situation that a post-baseline average for a quarter was missing the last available quarter prior was carried forward. For the fourth quarter, each deferasirox group was compared to placebo by 1-sided t-tests using Dunnett's adjustment for multiple comparisons to the placebo control group (family-wise type I error rate 0.025). the 2 deferasirox groups were compared by means of a 2-sided t-test at a significance level of 5%.

The correlation of LIC versus serum ferritin at baseline was assessed as well as the correlation of relative change in LIC versus relative change in serum ferritin at week 24 and week 52. The effect of dose increase was evaluated by summarizing the last LIC value after the Week 24 LIC assessment and the last value before or at the Week 24 LIC assessment with descriptive statistics by treatment group and separately for patients with and without increase. Patient subgroup analyses were also performed.

Analyses of exploratory haematological and iron metabolism parameters observed values (and changes from baseline) averaged at baseline, Month 3, Month 6, Month 9, Month 12 and last available month were summarized by descriptive statistics and in figures showing means and 95% confidence intervals. Total serum iron, observed value (and changes from baseline) averaged at baseline, monthly average and last available month were summarized similarly as were serum erythropoietin, plasma hepcidin and growth differentiation factor (GDF 15).

Results

Participant flow



Source: [Study A2209-Table 14.1-1.1]

Recruitment

Study centres were: Greece (2), Italy (6), Lebanon (1), Malaysia (4), Taiwan (1), Thailand (4), Turkey (4), UK (1) and USA (1). The First patient was enrolled on 24 November 2008 and the last patient completed on 22 June 2011.

Conduct of the study

There were three protocol amendments.

Baseline data

The median age in the 5 mg/kg/day deferasirox, 10 mg/kg/day deferasirox and combined placebo groups were 33, 31 and 32 years respectively. Twenty-one (12.7%) patients were <18 years old and only 1 (0.6%) was ≥65 years old. The ratio of males to females was nearly equal across treatment groups. The main underlying diseases were beta-thalassemia (95 patients, 57.2%) and HbE beta-thalassemia (49 patients, 29.5%). Eighty-eight (53.0%) patients were splenectomised, 6 (3.6%) had history of hepatitis of any form, and 145 (87.3%) had transfusion experiences more than 6 months prior to the start of study.

Table 2 – Baseline values of LIC and serum ferritin (FAS)

	Deferasirox 5 mg/kg/day N=55	Deferasirox 10 mg/kg/day N=55	Placebo Any dose N=56
LIC at baseline (mg Fe/g dw)			
n	55	55	55
Mean (SD)	13.11 (7.290)	14.56 (7.921)	15.94 (10.845)
Median	11.70	11.70	13.00
Range	2.6 - 38.6	5.0 - 32.8	5.0 - 49.1
Baseline LIC group, n (%)			
<5 mg Fe/g dw	1 (1.8)	0	0
5 - 7 mg Fe/g dw	9 (16.4)	8 (14.5)	13 (23.2)
>7 - 15 mg Fe/g dw	31 (56.4)	26 (47.3)	20 (35.7)
>15 mg Fe/g dw	14 (25.5)	21 (38.2)	22 (39.3)
Missing	0	0	1 (1.8)
Serum ferritin at baseline (µg/L)			
n	55	55	56
Mean (SD)	1140.7 (804.93)	1173.9 (684.37)	1305.1 (1017.08)
Median	988.0	1014.5	994.3
Range	370 - 5609	342 - 4224	304 - 6419
Baseline serum ferritin group, n (%)			
≤300 µg/L	0	0	0
>300-500 µg/L	5 (9.1)	4 (7.3)	8 (14.3)
>500-1000 µg/L	24 (43.6)	23 (41.8)	20 (35.7)
>1000-2500 µg/L	23 (41.8)	26 (47.3)	23 (41.1)
>2500-5000 µg/L	2 (3.6)	2 (3.6)	4 (7.1)
>5000 µg/L	1 (1.8)	0	1 (1.8)

Numbers analysed

156 patients planned, 166 randomized (55 at 5 mg/kg/day deferasirox, 55 at 10 mg/kg/day; 28 at 5 mg/kg/day placebo; 28 at 10 mg/kg/day placebo).

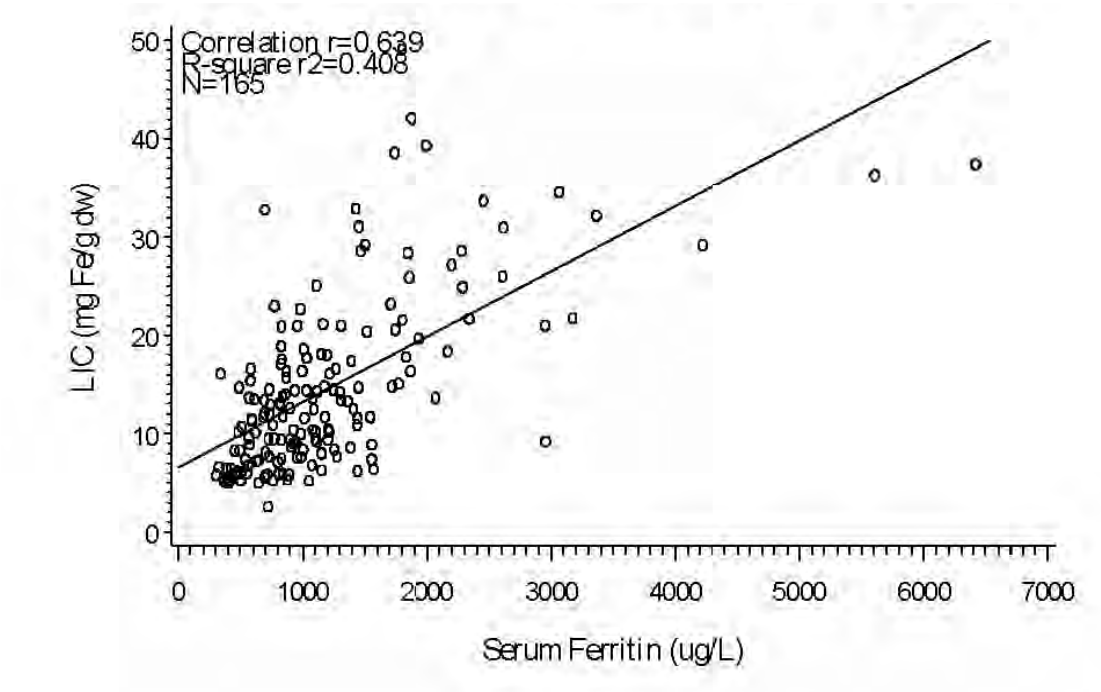
Outcomes and estimation

Table 3 – Absolute change in LIC (mg Fe/g dw) between baseline and Week 24 and Week 52 (FAS)

	Deferasirox 5 mg/kg/day (N=55)	Deferasirox 10 mg/kg/day (N=55)	Placebo Any dose (N=56)
Baseline			
N	55	55	55
Mean (SD)	13.11 (7.290)	14.56 (7.921)	15.94 (10.845)
Median	11.70	11.70	13.00
Range	2.6 - 38.6	5.0 - 32.8	5.0 - 49.1
Week 24 value*			
n	49	48	51
Mean (SD)	11.97 (7.990)	13.47 (9.128)	15.68 (10.429)
Median	9.60	10.00	13.40
Range	3.5 - 42.8	3.2 - 36.5	3.0 - 48.5
Absolute change from baseline to Week 24*			
N	49	48	51
Mean (SD)	-0.93 (3.097)	-0.90 (3.218)	-0.18 (3.050)
Median	-1.20	-1.30	0.20
Range	-7.2 - 9.8	-8.8 - 11.6	-8.8 - 8.4
Week 52 value*			
N	51	54	54
Mean (SD)	11.56 (7.928)	10.58 (7.667)	16.38 (10.606)
Median	9.50	8.80	12.80
Range	2.1 - 38.9	1.2 - 36.1	4.4 - 46.4
Absolute change from baseline to Week 52*			
N	51	54	54
Mean (SD)	-1.85 (3.078)	-3.78 (4.150)	0.26 (3.501)
Median	-2.00	-3.30	0.05
Range	-9.1 - 6.7	-12.0 - 4.8	-8.1 - 10.7

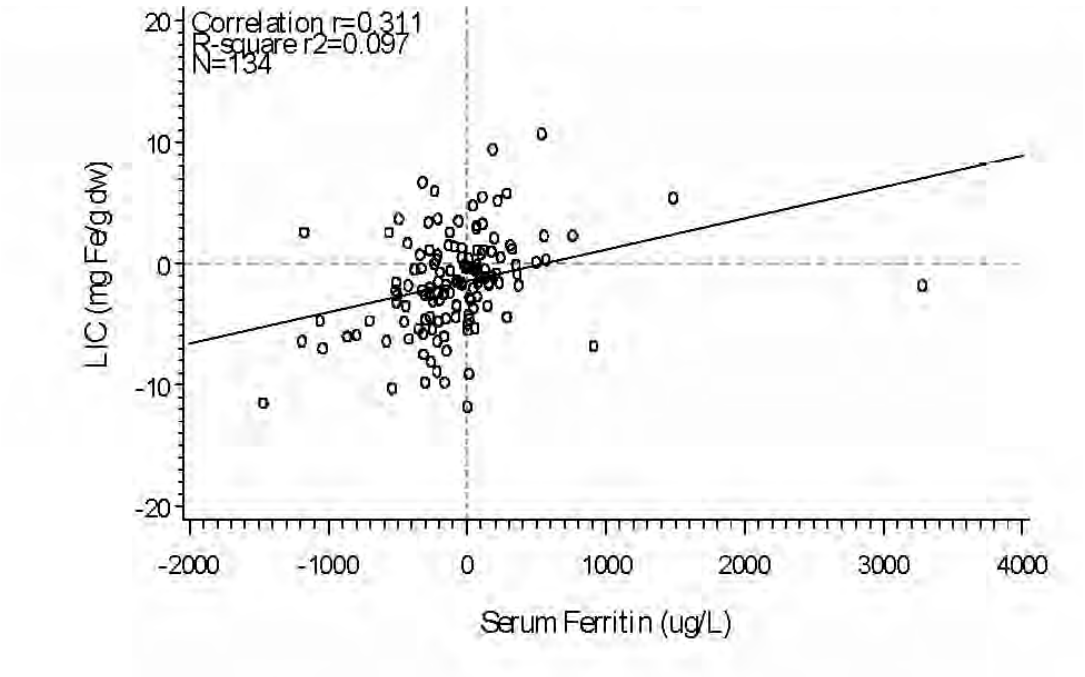
*The last available post-baseline LIC was carried forward if no LIC value was available at Week 24 or Week 52.

At each considered timepoint, only patients with both baseline and post-baseline values were summarized.



Note: the figure only includes patients with LIC and serum ferritin value at the respective time point.

Figure 1 - Correlation analysis for LIC versus serum ferritin (Full Analysis Set)
Baseline LIC versus baseline serum ferritin, linear regression



Note: the figure only includes patients with LIC and serum ferritin value at the respective time point.

Figure 2 - Correlation analysis for LIC versus serum ferritin (Full Analysis Set)
Week 52 LIC difference to baseline versus Week 52 serum ferritin difference to baseline, linear regression

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 4 – Summary of Efficacy for trial CICL670A2209

Title: A Randomized, Double-blind, Placebo-controlled, Phase II Study to Evaluate Efficacy and Safety of Deferasirox in Non-transfusion-dependent Thalassemia Patients With Iron Overload (THALASSA)				
Study identifier	CICL670A2209			
Design	Treatment, Parallel Assignment, Double Blind, Randomized			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months not applicable 12 months	
Hypothesis	Superiority			
Treatments groups	DFX 5		Deferasirox 5 mg/kg/day starting dose with option to dose increase to 10 mg/kg/day. Duration: 52 weeks, number randomized: 55	
	DFX 10		Deferasirox 10 mg/kg/day starting dose with option to dose increase to 20 mg/kg/day. Duration: 52 weeks, number randomized: 55	
	Placebo		Matching placebo dose. Duration: 52 weeks, number randomized: 56	
Endpoints and definitions	Primary endpoint	LIC change	Change in liver iron concentration (LIC, mg Fe/g dry weight) from baseline at week 52	
	Secondary endpoint	Serum ferritin change	Change in Serum Ferritin (SF, µg/l) between Baseline and Fourth Quarter	
	Exploratory endpoint	LIC response (decrease ≥3 mg)	Percentage of patients with an LIC decrease ≥ 3 mg Fe/g dw at week 52	
	Exploratory endpoint	LIC response (decrease ≥30%)	Percentage of patients with an LIC decrease ≥ 30% at week 52	
	Exploratory endpoint	LIC response (end of study LIC value <5 mg)	Percentage of patients achieving an LIC value <5 mg Fe/g dw at week 52	
	Exploratory endpoint	LIC response (end of study LIC value <3 mg)	Percentage of patients achieving an LIC value <3 mg Fe/g dw at week 52	
Database lock	27-July-2011			
Results and Analysis				
Analysis description	**Primary Analysis – LIC change**			
Analysis population and time point description	Full Analysis Set Week 52			
Descriptive statistics and estimate variability	Treatment group	DFX 5	DFX 10	Placebo
	Number of subjects	51	54	54
	LIC change (Least squares means, LSM)	-1.95	-3.80	0.38
	Standard Error	0.500	0.484	0.486
Effect estimate per	Primary endpoint	Comparison groups	DFX 10 vs Placebo	

comparison		LSM difference	-4.18	
		Standard Error	0.687	
		P-value	<0.001*	
		Comparison groups	DFX 5 vs Placebo	
		LSM difference	-2.33	
		Standard Error	0.700	
		P-value	0.001*	
		Comparison groups	DFX 10 vs DFX 5	
		LSM difference	-1.85	
		Standard Error	0.695	
		P-value	0.009 **	
Notes	* One-sided p-value with critical alpha-level 0.025 adjusted for multiplicity by Dunnett's method ** Two sided p-value with critical alpha-level 0.05; Only tested when both deferasirox arms were significantly better than placebo.			
Analysis description	**Secondary analysis – Serum ferritin change**			
Analysis population and time point description	Full Analysis Set Quarter 4 (Q4)			
Descriptive statistics and estimate variability	Treatment group	DFX 5	DFX 10	Placebo
	Number of subjects	55	55	56
	Serum ferritin change (Least squares means, LSM)	-120.69	-222.00	114.54
	Standard Error	41.759	41.759	41.384
Effect estimate per comparison	S2	Comparison groups	DFX 10 vs Placebo	
		LSM difference	-336.54	
		Standard Error	58.791	
		P-value	<0.001*	
		Comparison groups	DFX 5 vs Placebo	
		LSM difference	-235.24	
		Standard Error	58.791	
		P-value	<0.001*	
		Comparison groups	DFX 10 vs DFX 5	
		LSM difference	-101.31	
		Standard Error	59.056	
		P-value	0.088 **	
Notes	* One-sided p-value with critical alpha-level 0.025 adjusted for multiplicity by Dunnett's method ** Two sided p-value with critical alpha-level 0.05; Only tested when both deferasirox arms were significantly better than placebo.			
Analysis description	**Supportive analysis – LIC response (decrease ≥3 mg)**			
Analysis population and time point description	Full Analysis Set Week 52			
Descriptive statistics and estimate variability	Treatment group	DFX 5	DFX 10	Placebo
	Number of subjects	55	55	56
	LIC response rate n (%)	18 (32.7%)	31 (56.4%)	6 (10.7%)

Effect estimate per comparison	Supportive analysis – LIC response	Comparison groups	DFX 10 vs Placebo	
		* Odds ratio	16.3	
		95% confidence interval	5.213, 50.752	
		Comparison groups	DFX 5 vs Placebo	
		* Odds ratio	6.7	
		95% confidence interval	2.118, 21.080	
Notes	* Estimates obtained from a logistic regression model with treatment regimen and baseline LIC as explanatory variables. Ratio greater than 1 favors deferasirox			
Analysis description	**Supportive analysis – LIC response (decrease ≥30%)**			
Analysis population and time point description	Full Analysis Set Week 52			
Descriptive statistics and estimate variability	Treatment group	DFX 5	DFX 10	Placebo
	Number of subjects	55	55	56
	LIC response rate n (%)	14 (25.5%)	27 (49.1%)	1 (1.8%)
Analysis description	**Supportive analysis – LIC response (end of study LIC value <5 mg)**			
Analysis population and time point description	Full Analysis Set Week 52			
Descriptive statistics and estimate variability	Treatment group	DFX 5	DFX 10	Placebo
	Number of subjects	55	55	56
	LIC response rate n (%)	8 (14.5%)	15 (27.3%)	2 (3.6%)
Analysis description	**Supportive analysis – LIC response (end of study LIC value <3 mg)**			
Analysis population and time point description	Full Analysis Set Week 52			
Descriptive statistics and estimate variability	Treatment group	DFX 5	DFX 10	Placebo
	Number of subjects	55	55	56
	LIC response rate n (%)	1 (1.8%)	5 (9.1%)	0 (0.0%)

Supportive study ICL670A2202

Study ICL670A2202 was an open label, multi-centre, dose-escalation study of ICL670 consisting of 4 planned dose levels: dose level 1 (5 mg/kg/day), dose level 2 (10 mg/kg/day), dose level 3 (15 mg/kg/day) and dose level 4 (20 mg/kg/day). All patients received treatment for 24 weeks in core study and an additional 6 month in the extension phase. Enrolment into dose level 2, 3 and 4 was based on the data generated and safety review by MAH and DMC from the previous dose level.

The primary objective of this trial was to explore the safety of deferasirox (dose range 5 to 20 mg/kg/day) in adult hemochromatosis patients homozygous for the C282Y mutation, with iron overload. The secondary objectives were to explore the effect of ICL670 on serum ferritin and to characterize the pharmacokinetics of deferasirox in patients with hereditary hemochromatosis.

At least 40 patients were planned to be treated. Forty nine patients were recruited into the study, out of which 37 patients completed the core study (10, 11 and 16 patients in the 5, 10 and 15 mg/kg/day doses, respectively). Out of the 37 patients completing the core study, 26 chose to continue with the

extension and 23 completed the extension study (9, 6 and 8 patients in the 5, 10 and 15 mg/kg/day doses, respectively).

The main efficacy variable was the effect of deferasirox on serum ferritin, especially the change in serum ferritin from baseline at 24 weeks and 48 weeks. The secondary efficacy variables consisted of further characterizing the effect of deferasirox on serum ferritin (longitudinal course and time to normalization) and pharmacokinetics of deferasirox.

The primary objective of this study was safety, with incidence and severity of adverse events being the primary endpoints.

As indicated in section 2.3.2, characterisation of the pharmacokinetics was conducted in order to obtain the trough values of deferasirox which were summarized descriptively and plasma concentrations were to be plotted over time by dose group.

Patient baseline demographics were comparable between treatment groups. The patient population was Caucasian consisting of mainly male patients, with a mean age of 50.6 years and mean BMI of 27.16 kg/m^2. The mean time since initial diagnosis of hemochromatosis was 3.1 years with a mean serum ferritin value of 1149.7 µg/L. In the core study, out of 49 patients, 37 (75.5%) completed the core study and the main cause for discontinuations were due to AEs (7/49, 14.3%).Out of the 26 patients who continued with the extension, 23 (88.5%) completed the extension study wherein there were 3 discontinuations - 2 due to AEs and 1 due to administrative problems.

Results of the main efficacy endpoint are presented in the table below.

Table 5 – Serum ferritin [µg/L] at baseline and end of core, by dose cohort (Per protocol population)

	5 mg/kg/day N=11	10 mg/kg/day N=15	15 mg/kg/day N=22
Baseline			
N	11	15	22
Mean (SD)	636.7 (378.72)	926.7 (358.86)	797.4 (400.62)
Median	511.5	859.0	633.5
Range	376 - 1729	447 - 1792	357 - 1600
End of core			
N	11	15	22
Mean (SD)	476.8 (317.62)	570.1 (427.29)	476.8 (447.35)
Median	433.0	405.0	265.5
Range	171 - 1191	172 - 1465	79 - 1621
Absolute change			
N	11	15	22
Mean (SD)	-159.9 (275.43)	-356.5 (321.09)	-320.6 (309.49)
Median	-185.0	-327.0	-309.3
Range	-538 - 502	-1143 - 280	-931 - 158
Percentage change			
N	11	15	22
Mean (SD)	-19.9 (53.94)	-40.9 (29.11)	-44.0 (34.70)
Median	-31.1	-52.8	-55.4
Range	-69 - 128	-87 - 25	-85 - 25

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH submitted this type II variation to extend Exjade to the treatment of chronic iron overload requiring chelation therapy in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.

Data are mainly taken from one pivotal and one supportive study.

The pivotal Study A2209 was a phase II randomised double blind placebo controlled study designed to assess the efficacy and the safety of deferasirox in NTDT patients (aged >10 years-old) with iron overload. One hundred and sixty-six (166) patients were included and followed during 52 weeks. The supportive study A2202 was designed to determine both safety and efficacy of deferasirox in a limited number of adult patients (49) with iron overload from hereditary hemochromatosis (HH). Results taken from this last study should however be taken with caution since the patient's population is not comparable to that studied in the pivotal study.

As the objective was to reverse iron overload, only patients with LIC ≥ 7 mg Fe/g dw and serum ferritin > 500 ng/mL should have been included and an active comparator should have been used as recommended by treatment guidelines issued by the Thalassaemia International Federation (2007). The primary endpoint should have been a success rate (responders analysis).

The non-inferiority of Exjade against deferoxamine has not been formally demonstrated as no direct comparison is available due to the design of the study. Advantages of an orally available chelator are acknowledged, but, iron burden reversal/prevention in this indication is probably obtained with relatively short treatments. Advantage of the oral route is in this context less convincing.

Efficacy data and additional analyses

Results of Study 2209 showed a decrease in iron overload in patients with NTDT. The effect seems dose-dependent.

However, based on the above considerations, without data on relative efficacy and safety profiles of deferasirox and deferoxamine, possible inferiority cannot be excluded. Therefore, similarly to the currently approved indication of Exjade in second-line treatment of TDT patients, the use of Exjade in NTDT patients should be restricted to the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate.

Finally, the indication on when it is convenient to start chelation therapy was based on predicted results and it was not soundly supported. The trend in serum ferritin by monthly evaluation may be helpful in monitoring the efficacy of the therapy, but it cannot substitute the direct measurement of iron overload in the target organs. Thus, the cut-off of ferritine levels >800 μg/L is not the preferred criterion to initiate chelation in NTDT patients and a direct evaluation of liver i.e. LIC and, eventually heart overload, assessment by MRI is a better element to decide when to start iron chelation treatment and to monitor iron overload risk.

As the MAH no longer claimed any prevention of overload in NTDT, and considering that maintenance after successful treatment is secondary prevention, Exjade should be approved only to correct iron overload in NTDT with treatment being interrupted as soon as correction is obtained.

2.4.3. Conclusions on the clinical efficacy

Study A2209 results showed a decrease in iron overload in patients with NTDT. However, due to the lack of comparison with deferoxamine the use of Exjade in NTDT should be limited when deferoxamine therapy is contraindicated or inadequate.

2.5. Clinical safety

The safety profile in this dossier is primarily based on data from Study A2209 as well as the supportive safety data from the core and core plus extension populations of Study A2202/E.

Patient exposure

In ***study A2209***, a total of 166 patients were randomized: (i) 110 patients were treated with deferasirox 5 or 10 mg/kg/day, and (ii) 56 were treated with placebo 5 or 10 mg/kg/day.

The mean duration of exposure ranged from 11.4 months in the 5 mg/kg/day deferasirox group to 11.8 months in the 10 mg/kg/day placebo group. The majority of patients had at least 9 months of exposure (89.1% of patients in each deferasirox group, and 94.6% of patients in the combined placebo group).

A majority of patients (89.2%) completed the study. The rate of discontinuation was slightly higher in the deferasirox groups (12.7% and 10.9% of patients in the 5 and 10 mg/kg/day groups, respectively) compared to 8.9% of patients in the combined placebo group. The major reasons for discontinuation were AEs, abnormal laboratory values and withdrawal of consent, combined as 3 (5.5%), 5 (9.1%), and 4 (7.1%) patients in the deferasirox 5 mg/kg/day, 10 mg/kg/day and combined placebo groups, respectively. Patients lost to follow-up were 3 (5.5%) and 1 (1.8%) in deferasirox 5 mg/kg and 10 mg/kg, treatment groups, respectively.

The proportion of patients with a dose increase based on the Week 24 LIC assessment was slightly lower in the deferasirox 10 mg/kg/day group (45.5%) and in the deferasirox 5 mg/kg/day group (47.3%) than in the combined placebo group (53.6%). According to the MAH, this could be explained by the fact that more patients in the active treatment groups were responding, and hence, a lesser percentage needed a dose increase compared to placebo. As a consequence of the dose increase, the average actual daily dose tended to be above the randomized dose in all treatment groups: mean (±SD) was 5.6 (±1.4), 11.5 (±2.93), 5.9 (±1.4) and 11.8 (±2.88) mg/kg/day for the deferasirox 5 mg/kg/day group, deferasirox 10 mg/kg/day group, placebo 5 mg/kg/day group, and placebo 10 mg/kg/day group, respectively.

The safety population of ***Study A2202/E*** included all patients (N=49) who received at least one dose of study drug within the core study and had at least one safety assessment within the core study.

The extension safety population included all patients (N=26) who received at least one dose of study drug within the extension study and had at least one safety assessment within the extension study. Safety was evaluated for the core period using the safety population, and for the core plus extension period using the extension safety population.

Two-thirds of the patients in the A2202/E Safety Population were male, and all patients were Caucasian (consistent with the genetic patterns of C282Y homozygous hemochromatosis). Patients were older than in Study A2209: the median age was 53 years with no patients <18 years of age (range 19 to 87).

The mean duration of exposure in the core was 18.3 weeks: 22.2 weeks in the 5 mg/kg/day group, 19.0 weeks in the 10 mg/kg/day group and 15.9 weeks in the 15 mg/kg/day group. The mean duration of exposure in the core plus extension for the extension safety population was 40.4 weeks: 43.4 weeks in the 5 mg/kg/day group, 48.4 weeks in the 10 mg/kg/day group and 33.6 weeks in the 15 mg/kg/day group.

Adverse events

Study A2209

The system organ classes (SOC) with the highest incidence of AEs overall (at least 20% in any treatment group) were infections and infestations, gastrointestinal disorders, general disorders and administration site conditions, nervous system disorders, respiratory, thoracic and mediastinal disorders, and musculoskeletal and connective tissue disorders.

The incidence of AEs in the SOC infections and infestations and nervous system disorders were similar between each deferasirox arm and its matching placebo arm. For the SOC of gastrointestinal disorders, the overall incidences were higher with placebo than with deferasirox and the incidences were higher with the higher doses.

The number of patients with AEs per preferred term was small. Overall, the most frequent AEs (at least 10% in any deferasirox or the combined placebo group) were headache, upper respiratory tract infection, oropharyngeal pain, pyrexia, rash, diarrhoea, and nausea.

Headache, rash, fatigue, rhinitis, and dyspepsia were more frequent (at least 5% difference) in the 10 mg/kg/day deferasirox group than in the 5 mg/kg/day deferasirox group. Upper abdominal pain and dyspepsia occurred in at least one deferasirox group and not on placebo. Upper respiratory tract infection and pyrexia were more frequently reported in either placebo group compared to either deferasirox group.

Study A2202/E

In the *Core phase*, the majority of patients in all dose levels reported at least one AE (95.9% overall).

The SOC with the highest incidence of AEs (at least 20% of all patients) was gastrointestinal disorders, followed by infections and infestations, musculoskeletal and connective tissue disorders, investigations, nervous system disorders and general disorders and administration site conditions.

Twenty-five of the 26 patients (96.2%) in the *Extension* safety population reported at least one AE during core plus extension. The frequencies were comparable to those reported in the core for the Safety population. The highest incidence of AEs (at least 20% of all patients) was reported for the SOCs gastrointestinal disorders (65.4%), followed by musculoskeletal and connective tissue disorders (50%), infections and infestations (42.3%), investigations (38.5%), general disorders and administration site conditions (34.6%), skin and subcutaneous tissue disorders (30.8%) and nervous system disorders (26.9%) and eye disorders (23.1%).

By preferred term, the most frequent AEs overall (at least 10%) in the *core phase* were diarrhoea, headache, nausea, abdominal pain, back pain, increased blood creatinine, increased ALT, rash, flatulence and nasopharyngitis. In general, the frequencies of AEs were lower in the 5 mg/kg/day group than in the 10 mg/kg/day or 15 mg/kg/day groups. Some preferred terms (e.g., headache, nausea and rash) were reported more frequently in the 15 mg/kg/day group than in the 10 mg/kg/day (or 5 mg/kg/day) group, whereas the incidence of other preferred terms (e.g., diarrhoea, abdominal pain) were similar between the 15 mg/kg/day and 10 mg/kg/day groups (but lower in the 5 mg/kg/day group).

By preferred term, the most frequent AEs in the *core plus extension* (at least 15%) were diarrhoea, back pain, increased blood creatinine, headache, arthralgia, nausea, upper respiratory tract infection, fatigue and rash.

Serious adverse event / deaths / other significant events

Study A2209

There were no *deaths* in Study A2209.

Twenty-four patients reported s*erious adverse events* (SAEs). The overall incidences of SAEs in Study A2209 were comparable between deferasirox and placebo, with slightly higher incidences being reported in the 10 mg/kg/day dose groups than in the 5 mg/kg/day dose groups both for deferasirox and placebo.

SAEs considered related to study drug by the investigator were reported for 4 patients: 3 in the deferasirox 5 mg/kg/day group (abdominal pain, cellulitis and hepatotoxicity), and one in the deferasirox 10 mg/kg/day group (pruritus and rash). The patients experiencing the abdominal pain and cellulitis SAEs resolved and the patients continued on the study. The hepatotoxicity event occurred at the end of the core treatment and was ongoing as of the last report. The patient who experienced pruritus/rash SAEs discontinued study treatment.

AEs of special interest were analysed for Study A2209 based on signals observed during previously conducted clinical MAH has described the 9 groups of terms that comprise the adverse events of special interest in this dossier. By grouped term, each group had no more than 2 patients with one AE each.

In addition, regarding *skin rash*, few patients met the event criteria for severe or persistent skin rash: 1 patient in the 5 mg/kg/day deferasirox group, 3 patients in the 10 mg/kg/day deferasirox group, and 1 patient in the placebo 5 mg/kg/day group. One of the patients in the 10 mg/kg/day deferasirox group had 2 episodes of severe or persistent rash, the others had a single episode each. Study drug was interrupted within 10 days of event onset for 2 of the patients in the 10 mg/kg/day deferasirox group. Two patients, both in the 10 mg/kg/day deferasirox group, had rash events that were ongoing at end of study. One patient had SAEs of severe rash and pyrexia for which he was hospitalized. The events were suspected to be related to study drug. Study drug was later discontinued due to rash and pruritus. The other patient had mild macular rash that was not suspected to be related to study drug that had started on Day 57 and was ongoing at end of study.

Study A2202 / E

No *deaths* occurred either in the core study or in the extension study.

One *SAE* (prostate cancer recurrent) was reported in the extension study, while none were reported in the core study. The patient had a history of prostate cancer and prostectomy. He was diagnosed with recurrence of prostate cancer on day 28 of the core phase. The patient received medical treatment and radiotherapy and recovered on day 119.

In the core, moderate *skin rash* was reported for 2 patients, and severe skin rash was reported for 1 patient (all 3 were in the 15 mg/kg/day group). No additional events were reported in the extension. Median time to event could not be estimated due to low number of events. The durations of the 2 events of moderate skin rash were 11 and 21 days, respectively, and of the severe skin rash was 5 days.

Laboratory findings

For Study A2209, notably abnormal values in key safety laboratory parameters post-baseline are summarised in the table below.

Table 6 – Post-baseline laboratory results meeting criteria for notable values (Study A2209 – Safety set)

	Deferasirox 5 mg/kg/day N=55 n (%)	Deferasirox 10 mg/kg/day N=55 n (%)	Placebo 5 mg/kg/day N=28 n (%)	Placebo 10 mg/kg/day N=28 n (%)	Placebo Any dose N=56 n (%)
Platelet count (<100 x 10^9/L)	3 (5.5)	3 (5.5)	4 (14.3)	2 (7.1)	6 (10.7)
Absolute neutrophils (<1.5x10^9/L)	3 (5.5)	2 (3.6)	2 (7.1)	1 (3.6)	3 (5.4)
ALT (>5xULN and >2xbaseline)	0	0	0	1 (3.6)	1 (1.8)
AST (>5xULN and >2xbaseline)	0	1 (1.8)	0	1 (3.6)	1 (1.8)
Serum creatinine (>33% increase from baseline and >ULN at ≥ 2 consecutive post-baseline values)	0	3 (5.5)	0	0	0
Creatinine clearance (< 60 mL/min at ≥ 2 consecutive post-baseline values	1 (1.8)	1 (1.8)	0	0	0
Urinary protein/creatinine ratio (≥ 1.0 mg/mg at ≥ 2 consecutive post-baseline values)	1 (1.8)	0	0	0	0

For two consecutive values, measurements must be at least 7 days apart. Events were counted in the period in which the second measurement was taken.

Percentages are relative to the number of patients with evaluable criterion.

Source: [Study A2209-Table 12-14]

Haematology

In *Study A2209*, there were no patients with AEs related to decreases in platelet or neutrophil counts. No relevant differences were observed over time across the treatment groups for any of the haematology parameters assessed. Subgroup analyses of haematology parameters did not reveal any relevant differences for age, gender, or race.

In the *core study A2202/E,* there were no shifts to notable values for platelets (<100 x 10^9/L) or neutrophils (<1.5 x 10^9/L) in the core study and no clinically relevant changes from baseline. Shifts from low/normal at baseline to high were infrequent for most haematology parameters and not considered clinically relevant by the MAH.

In the *core+extension*, there were no patients with a shift to a notable value for platelets (platelet <100 x 10^9/L). One patient with a low neutrophil count at baseline had at least 2 consecutive neutrophil values <1.5 x 10^9/L during the core plus extension, and 4 patients with normal neutrophil counts at baseline had a neutrophil value (but not consecutive measurements) that was <1.5 x 10^9/L during the core plus extension.

Clinical Chemistry

With the exception of changes in parameters of renal and hepatic function (discussed below), no relevant differences in clinical chemistry parameters were observed over time across the treatment groups in *Study A2209*.

No relevant changes were noted for the other clinical chemistry parameters in *study A2202/E*. A slight increase in creatinine that was more pronounced with the higher doses was noted by Week 4; creatinine levels remained stable thereafter across all dose groups. No further change in creatinine levels was apparent with longer follow-up in the extension study.

In the core study, shifts from low/normal at baseline to high were most frequently observed for the following parameters: creatinine (54.2%), ALT (41.7%), AST (34.1%), and bilirubin (15.2%). The shifts tended to be less frequent in the 5 mg/kg/day dose group than in the 10 mg/kg/day or 15 mg/kg/day dose groups. Similar results were observed in the extension.

Renal function

Study A2209

Analysis of AEs of special interest revealed only a few patients with AEs related to renal function. None were severe, and only one event (moderate proteinuria) led to discontinuation of study drug.

Proteinuria was reported for 2 patients: One mild proteinuria after 2 months on deferasirox treatment (5 mg/kg/day) which resolved after a week without intervention. This patient had slightly elevated UPCR at baseline; One moderate proteinuria following dose escalation of deferasirox to 10 mg/kg/day which led to discontinuation of study drug (event ongoing).

As indicated in the above table, notable abnormalities in creatinine, creatinine clearance and/or UPCR were reported for 5 patients (all on deferasirox treatment).

Resolution was evident for all the above cases except one patient for whom the decrease in creatinine clearance occurred towards the end of the study and there were no further study visits. None of these events led to discontinuation of study drug.

Evaluation of shifts for additional categories of creatinine, creatinine clearance and UPCR showed that these shifts were infrequent overall, and occurred across treatment groups. The frequencies of shifts were similar in the placebo groups and the 5 mg/kg/day deferasirox group, and slightly higher in the 10 mg/kg/day deferasirox group.

Categorical analyses of relative changes in creatinine clearance from baseline to last value were conducted. Most patients had an increase or a decrease in creatinine clearance falling into either the 0 to 10% or 10 to 20% categories. The distribution of categorical changes in CrCl was similar in the deferasirox and the placebo groups. Decreases of >20% were infrequent: 2 patients (3.6%) and 9 patients (16.4%) in the deferasirox 5 and 10 mg/kg/day groups, and 4 patients (7.1%) in the combined placebo group).

Serum creatinine levels and creatinine clearance remained relatively constant over time across deferasirox and placebo groups. UPCR values fluctuated over time in all treatment groups without showing any clear trends. Evaluating creatinine clearance by average actual daily dose showed similar results for placebo and the lowest deferasirox dose category, and a slightly higher decrease in creatinine clearance with higher deferasirox doses, although it remained within the boundaries of the mean intra-subject variability of 18.7% in creatinine clearance assessment (Toffaletti et al 2008). At Month 12, the relative change from baseline in creatinine clearance was as follows: -3.1±12.8% for placebo, -2.1±13.5% for deferasirox >0 to <7.5 mg/kg/day, -5.8±13.9% for deferasirox ≥ 7.5 to ≤ 12.5 mg/kg/day, and -9.1±13.1% for deferasirox >12.5 to ≤ 17.5 mg/kg/day.

Study A2202/E

A total of 14 patients had AEs related to renal function (renal impairment, blood creatinine increased, and/or creatinine renal clearance decreased) during core and/or extension treatment.

By dose group, these AEs were reported for 1 patient (9.1%), 6 patients (40.0%) and 7 patients (30.4%) in the 5, 10 and 15 mg/kg/day groups, respectively.

Four patients experienced renal impairment (2 patients in the 10 mg/kg/day group and 2 patients in the 15 mg/kg/day group; one of the latter had also creatinine increased). One of these 4 patients

(10 mg/kg/day group) discontinued the study due to renal impairment). In addition, 2 patients had dose adjustments and no action was needed for the fourth patient. None of these events were severe and all resolved.

Eleven patients experienced blood creatinine increased (including the patient who also had renal impairment mentioned above). One patient (10 mg/kg/day group) also had decreased creatinine clearance (this patient had 3 episodes of increased creatinine) Most events were mild in intensity. Study drug was temporarily interrupted for 9 of the 11 patients due to increased creatinine. The events of increased creatinine resolved for 10 of the 11 patients.

In the core part, creatinine levels increased slightly with treatment in all dose groups and remained stable thereafter. Eleven of 48 patients (22.4%) with normal creatinine at baseline had 2 consecutive values during the study that were >33% increased from baseline and >ULN (5 patients were in the 10 mg/kg/day group and 6 patients were in the 15 mg/kg/day group).

A total of 77.6% of patients had a decrease in creatinine clearance (centering mainly on the 0 to 10% category, but also in the 10 to 20% and 20 to 30% categories), and 22.4% had an increase. The shift in patients in the 5 mg/kg/day group tended to be smaller (mostly <10% in either direction) than in the 10 or 15 mg/kg/day dose groups. Decreases of >20% were seen for 2 patients (18.2%), 4 patients (26.7%), and 6 patients (26.1%) in the 5, 10 and 15 mg/kg/day dose groups, respectively

Creatinine levels remained relatively stable; there were 7 patients (26.9%) in the extension safety population with creatinine >33% increased from baseline and > ULN on 2 consecutive visits at least 7 days apart.

A total of 92.3% of patients had a decrease in creatinine clearance (mostly in the 0 to 10%, 10 to 20%, 20 to 30% categories). Decreases of >20% were seen for 2 patients (22.2%), 2 patients (33.3%), and 4 patients (36.4%) in the 5, 10 and 15 mg/kg/day dose groups, respectively.

Hepatic function

Study A2209

ALT and AST decreased slightly over time in patients on deferasirox, which was more evident in the higher dose group. Shifts from below ULN at baseline to above ULN occurred in about a third of the patients with normal baseline values, and there were no relevant differences between deferasirox- and placebo-treated patients (respectively 30 and 35%). There is no cases of ALT >5N in deferasirox groups.

Two patients (one in the 10 mg/kg/day deferasirox group and one on placebo) had shifts to AST and / or ALT >5 x ULN and >2x baseline.

One patent in the 10 mg/kg/day deferasirox group had an AST value of 457 U/L that met the criteria of notable abnormality. He also had ALT of 185 U/L, which did not meet the above criteria of notable, and was reported as an AE (SOC: Investigations) with suspected relationship to study drug.

One patient in the 10 mg/kg/day placebo group had a single occurrence of concurrent notable AST (228 U/L) and ALT (271 U/L) values. Neither ALT nor AST were reported as an AE for this patient.

Analysis of AEs of special interest revealed 3 patients with AEs related to hepatic function (one with hepatotoxicity, and 2 with increased ALT or AST). No patient in Study A2209 discontinued due to increases in transaminases.

Study A2202/E

One patient from the 15 mg/kg/day group had an ALT value >5 times the ULN. No such value occurred in the 5 and 10 mg/kg/day groups. No AST value >5 times the ULN occurred for any of the extension safety population patients. The majority of increases in AST and ALT occurred in the 15 mg/kg/day dose cohort, and in all cases where available, follow-up lab values returned to within baseline range within a period of 2-4 weeks, usually in conjunction with a dose interruption.

In Study A2202/E, increased ALT, AST and/or transaminase were reported as AE(s) for 9 patients (8 patients during the core and one additional patient during the extension). Most of the events were mild or moderate in intensity and considered related to study drug.

By dose group, these AEs were reported for 3 patients (20.0%) and 5 patients (21.7%) in the 10 and 15 mg/kg/day groups, respectively during core treatment and 1 additional patient in the 5 mg/kg/day group during the extension. Four patients discontinued, 4 patients had temporary interruption of study drug, and no change in study drug was required for 1 patient. The events resolved for all except one of the patient who discontinued. Two of the patients with increased ALT had also increased AST reported as AE (one of them discontinued). Elevated serum transaminase led to discontinuation during extension treatment for one patient with concurrent renal impairment. In addition, one patient in the 10 mg/kg/day group had hepatic function abnormal reported as an AE. The event was mild, not suspected to be related to study drug, and resolved in 3 weeks without intervention.

One of the above-mentioned patients had dose escalation of study drug (from 5 mg/kg/day to 10 mg/kg/day) about a month prior to the event during extension treatment; none of the other patients had dose escalation during the core or extension of the study.

ECGs, vital signs, body weight and physical examinations

In *Study A2209*, evaluation of vital signs and weight revealed no relevant differences between the treatment groups in terms of notable abnormalities or any relevant changes in these parameters from baseline. On ECG, 2 patients on the deferasirox 5 mg/kg/day group and one patient on the deferasirox 10 mg/kg/day group had new or worsened clinically significant abnormalities; none was suspected to be related to study drug. Audiometric test, and ocular examinations showed no notable abnormalities.

In *Study A2202/E*, 3 patients had AEs related to lens opacities, retinal changes and optic neuritis: 2 patients with cataract (both in the core), and one patient with maculopathy (in extension).

AEs related to hearing loss were reported for 5 patients. All hearing loss-related AEs were mild, none warranted a change in study medication and all were ongoing at the end of study (i.e. core or extension). Two patients (both in the 15 mg/kg/day groups) had hearing loss-related AEs that were considered related to study medication (one neurosensory hypoacusis (mild) and one hypoacusis (mild)).

Safety in special populations

AEs and laboratory results were analysed by demographic subgroups (gender, age, race), by baseline LIC and SF categories, and by underlying disease subgroups in ***Study A2209***. No relevant differences were observed in the safety profile for deferasirox across demographic subgroups, underlying disease, or baseline LIC or SF categories, although the number of patients in each subgroup was small. No relevant differences were seen in the incidence of AEs when comparing patients with and without a dose increase.

Study A2209 enrolled 21 patients who were <18 years old (6 and 7 patients in the deferasirox 5 and 10 mg/kg/day groups, respectively, and 8 patients in the combined placebo group). The number of severe AEs was comparable between paediatric and adult population in deferasirox groups.

Nausea occurred in two deferasirox-treated patients and one placebo-treated patient. Abdominal discomfort occurred in one placebo-treated patient. Rash occurred in three deferasirox-treated patients, and in one placebo-treated patient.

No patients <18 years of age discontinued due to an AE. Two deferasirox-treated paediatric patients had a dose adjustment or interruption treatment due to an AE.

None of the deferasirox- or placebo-treated paediatric patients showed : an >33% increase in serum creatinine above ULN on two consecutive occasions; a creatinine clearance values below 60 mL/min on two consecutive occasions or a UPCR > 1mg/mg on 2 consecutive occasions.

One deferasirox-treated paediatric patient had at least one episode of AST increased from normal to >ULN and ≤5xULN. Four placebo-treated paediatric patients had at least one episode of AST increased from normal to >ULN and ≤5xULN.

Two deferasirox-treated paediatric patient had at least one episode of ALT increased from normal to >ULN and ≤5xULN. Four placebo-treated paediatric patients had at least one episode of ALT increased from normal to >ULN and ≤5xULN.

None of the deferasirox- or placebo-treated paediatric patients had a decrease in absolute neutrophil count (ANC) below 1.5×10^9/L during the study.

No subgroup analyses were performed for **study A2202/E**. No pregnancies were reported in this study.

Discontinuation due to adverse events

Study A2209

Adverse events led to drug discontinuations in 8 patients. Two of these 8 patients discontinued due to pregnancy. Three patients (all on deferasirox) discontinued due to AEs considered related to study drug by the investigator: one patient with anaemia, one patient with proteinuria (after dose increase from 5 to 10mg/kg/day), and one patient with pruritus and rash (SAEs). The 3 remaining patients were a placebo treated patient with severe anaemia, a placebo-treated patient with optic neuritis (SAE) and a deferasirox 5 mg/kg/day-treated patient with a pelvic fracture (SAE).

The incidence of AEs requiring dose adjustment or interruption of study drug in Study A2209 was 21.8% and 18.2% for deferasirox 5 and 10 mg/kg/day groups, and 17.9% and 14.3% for placebo 5 and 10 mg/kg/day groups, respectively. Most preferred terms occurred in only one or two patients each. These are: blood creatinine increased, pyrexia, rash, anaemia, and influenza.

Study 2202/E

Out of the 8 discontinuations from the core study which occurred due to AEs (mainly increased transaminases), 5 occurred in the 15 mg/kg/day dose cohort (21.7%), while the remaining 3 (20%) occurred in the 10 mg/kg/day dose cohort. Two patients had increased transaminase (all in deferasirox 15 mg/kg/day); other preferred terms were reported for only 1 patient each.

Two discontinuations from the core plus extension study occurred due to AEs (diarrhoea and increased transaminases) in the 15 mg/kg/day dose cohort.

The incidence of AEs requiring a dose reduction or interruption was higher in the 15 mg/kg/day group (13 patients, 56.5%) and the 10 mg/kg/day group (6 patients, 40%) than in the 5 mg/kg/day group (1 patient, 9.1%). Most of these AEs were laboratory abnormalities (e.g., blood creatinine increased, ALT increased), or GI related (e.g., diarrhoea, nausea) and considered related to study drug. Renal impairment was reported for 2 patients; other preferred terms were reported for at most 1 patient each.

Similarly to the core, the incidence of AEs requiring a dose reduction or interruption in the core plus extension was higher in the 15 mg/kg/day group (6 patients, 54.5%) than in the 10 mg/kg/day group (2 patients, 33.3%) and in the 5 mg/kg/day group (2 patients, 22.2%). Most of these AEs were laboratory abnormalities (e.g., increased creatinine or increased ALT); other preferred terms were headache, or related to rash, renal function, or GI disorders. Most of these AEs were considered related to study drug.

2.5.1. Discussion on clinical safety

In general the safety profile was comparable to that already described for the other approved indications.

The most frequent AEs (at least 10% in any deferasirox treatment group) in the NTDT patients (target population) were headache, upper respiratory tract infection, oropharyngeal pain, pyrexia, and rash.

The overall adverse event profile was consistent with the known safety profile of Exjade and complications of underlying conditions. Both studies do not bring any new relevant information regarding the safety profile of Exjade. However, the number of young patients (aged of 10-18 years-old) with NTDT is too low to draw any firm conclusion on the safety in this subpopulation (n=13 in deferasirox groups + 8 in cross over group participating in the one-year study extension).

The renal risk with Exjade has been assessed. The planned duration of treatment in NTDT patients is still uncertain: firstly planned to be more or less one year, the median duration was established in study 2209 around 21 months (less than 2 years) depending of clinical features of the patients. In study 2209, to achieve the target LIC of 3 mg Fe/g dw in a patient with baseline LIC of 20mg/Fe/g dw, the mean treatment duration could reach 4.8 years [3.92 – 6.11] with a dose of 10mg/kg/day. One should consider the importance of renal risk in NTDT patients, with a long term exposure and especially in those patients in whom kidney function is often already compromised. It is difficult to assess whether renal toxicity can be manageable in these patients as the duration of treatment and dose tapering have not been addressed in the pivotal study. Indeed, one should keep in mind that deferasirox could be a long term treatment, and that renal dysfunction is a severe factor of morbidity. Available data do not allow affirming that there is a reversibility of the renal events associated with deferasirox use, after a drug interruption.

Overall, renal and hepatic toxicities with Exjade therapy persist and are not yet fully understood: increases in serum creatinine might be manageable with dose reduction/interruption but cases of acute renal failure, some requiring dialysis, have also been reported following use of deferasirox. Risk minimisations are in place with respect to these issues.

The risk of overchelation the NTDT population cannot be excluded in this population with moderate overload, especially when patients are exposed to 10mg/kg/day (even 20 mg/kg/day). The recommended doses and stopping rules when target LIC and SF were reached could be adequate to avoid this risk, and has been included in both SmPC and risk minimisation tools.

Study A2209 only included 21 patients (n=13 in deferasirox groups + 8 in cross over group participating in the one-year study extension) under 18 years old (ie 12,7% of patients included) which is very few to draw any firm conclusion on efficacy and safety in this population. Therefore, a close follow-up of these patients is essential and risk minimisation measures should be strengthened. The SmPC includes a specific warning concerning uncertainties on consequences of a long-term exposure in this category of patients

Specifically for paediatric population, a warning for prescribers on the necessity of closer monitoring of LIC and SF and on the uncertainties of the safety consequences in the long term treatment has been included in the risk minimization activities.

Furthermore, as an obligation to conduct post-authorisation measure, the MAH should conduct an observational study (cohort) for all paediatric NTDT patients over 10 years-old for whom deferoxamine is contra-indicated or inadequate (as the registry performed for patients between 2 and 5 years-old) in order to obtain long-term safety data from a significative sample of paediatic patients in real life. A specific section for paediatric NTDT patients in the future PSURs should also be provided.

2.5.2. Conclusions on the clinical safety

The CHMP considers the following measures necessary to address issues related to safety:

- The MAH should conduct an observational study (cohort) for all paediatric NTDT patients over 10 years-old for whom deferoxamine is contra-indicated or inadequate (as the registry performed for patients between 2 and 5 years-old) in order to obtain long-term safety data from a significative sample of paediatic patients in real life, with the following timeframe:
    - Submission of feasibility assessment: April 2013
    - Submission of protocol: after CHMP review of feasibility assessment
    - Annual updates on enrolment will be provided
    - Annual updates of 5-year results of patients enrolled will be provided.
    - Final Clinical study report to be submitted by June 2021

2.6. Risk management plan

The MAH submitted an updated Risk Management Plan within this variation procedure which included a risk minimisation plan.

Table 1. Summary of the risk management plan (including the changes related to the application presented highlighted)

Safety issues	**Agreed pharmacovigilance activities**	**Agreed risk minimisation activities**
Important identified risks		
Increased Serum creatinine	Routine pharmacovigilance activities including cumulative analysis in PSUR. Targeted follow-up of all serious SR, post-marketing surveillance study reports, reports from other programs where data are being handled as solicited, and all clinical trial SAE reports using a targeted questionnaire /	This item is appropriately communicated through current labeling: SPC Section 4.2 Posology and method of administration, 4.3 Contraindications, and 4.4 Special warnings and precautions for use. Relevant preferred terms are included as ADRs Section 4.8 Undesirable effects.

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
	checklist. PEM study. Studies involving sentinel site monitoring (Study ICL670A2301 and Study ICL670AFR01T). Renal mechanistic Study ICL670A2123(study enrolment closed after 11 of 16 planned patients). Study ICL670A2204 (including extension) Inclusion of renal monitoring in on-going and planned study protocols Expedited reporting to the EMA (including renal biopsies, see Section 2.2.1)	Enhanced Risk Minimization Activities (all are completed) Physician educational material (including survey). Patient booklet for monitoring laboratory test results (including survey). The surveys are completed Effectiveness assessment An investigation of compliance to risk minimization measures will be proposed
Acute renal failure	Routine pharmacovigilance activities including cumulative analysis in PSUR Targeted follow-up of all serious spontaneous reports, post-marketing surveillance study reports, reports from other programs where data are being handled as solicited, and all clinical trial SAE reports using a targeted questionnaire / checklist.	This item is appropriately communicated through current labeling: SPC Section 4.2 Posology and method of administration, 4.3 Contraindications, 4.4 Special warnings and precautions for use, 5.2 Pharmacokinetic properties and 5.3 Preclinical safety data. Relevant preferred terms are included as ADRs in SPC Section 4.8 Undesirable effects.
Renal tubular disorders (acquired Fanconi's syndrome)	Routine pharmacovigilance activities including cumulative analysis in PSUR Targeted follow-up of all serious spontaneous reports, post-marketing surveillance study reports, reports from other programs where data are being handled as solicited, and all clinical trial SAE reports using a targeted questionnaire / checklist.	This item is appropriately communicated through current labeling: SPC Section 4.2 Posology and method of administration, 4.3 Contraindications, 4.4 Special warnings and precautions for use, 5.2 Pharmacokinetic properties and 5.3 Preclinical safety data. Relevant preferred terms are included as ADRs in SPC Section 4.8 Undesirable effects.
Increased liver transaminases	Routine pharmacovigilance activities including cumulative analysis in PSUR. Targeted follow-up of all serious spontaneous reports, post-marketing surveillance study reports, reports from other programs where data are being handled as solicited, and all clinical trial SAE reports using a targeted questionnaire / checklist. PEM study.	This item is appropriately communicated through current labeling: SPC Section 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use, and 5.2 Pharmacokinetic properties. Relevant preferred terms are included as ADRs Section 4.8 Undesirable effects. Enhanced Risk Minimization Activities (all are completed) Physician education (including

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
	Studies involving sentinel site monitoring (Study ICL670A2301 and Study ICL670AFR01T). Inclusion of monitoring of hepatic function in ongoing and planned study protocols Expedited reporting to the EMA (including gallstones, see Section 2.2.1.	survey). Patient booklet for monitoring laboratory test results (including survey). The surveys are completed. Effectiveness assessment An investigation of compliance to risk minimization measures will be proposed
Gastrointestinal hemorrhage and ulcer; esophagitis	Routine pharmacovigilance activities including cumulative analysis in PSUR Targeted follow-up of all serious spontaneous reports, post-marketing surveillance study reports, reports from other programs where data are being handled as solicited, and all clinical trial SAE reports using a targeted questionnaire / checklist.	This item is appropriately communicated through current labeling: SPC Section 4.4 Special warnings and precautions for use, and 4.5 Interaction with other medicinal products and other forms of interaction. Relevant preferred terms are included as ADRs in SPC Section 4.8 Undesirable effects.
Hearing loss	Routine pharmacovigilance activities including cumulative analysis in PSUR Targeted follow-up of all serious spontaneous reports, post-marketing surveillance study reports, reports from other programs where data are being handled as solicited, and all clinical trial SAE reports using a targeted questionnaire / checklist. Study ICL670A2411. Inclusion of annual auditory monitoring in ongoing and planned clinical study protocols. Expedited reporting to the EMA (see Section 2.2.1).	This item is appropriately communicated through current labeling: SPC Section 4.4 Special warnings and precautions for use. Relevant preferred terms are included as ADRs in Section 4.8 Undesirable effects.

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Lens opacities, retinal changes, and optic neuritis	Routine pharmacovigilance activities including cumulative analysis in PSUR, for lens opacities, retinal changes, and optic neuritis. Targeted follow-up of all serious spontaneous reports, post-marketing surveillance study reports, reports from other programs where data are being handled as solicited, and all clinical trial SAE reports using a targeted questionnaire / checklist for lens opacities and cataract.. Studies ICL670A2204 (including extension) and ICL670A2411. Inclusion of ophthalmologic monitoring and annual ocular examination in ongoing and planned clinical study protocols. Expedited reporting to the EMA EMA of reports of cataract (see Section 2.2.1).	This item is appropriately communicated through current labeling: SPC Section 4.4 Special warnings and precautions for use, 5.3 Preclinical safety data. Relevant preferred terms are included as ADRs in Section 4.8 Undesirable effects.
Important potential risks		
Hepatic failure	Routine pharmacovigilance activities including cumulative analysis in PSUR Targeted follow-up of all serious spontaneous reports, post-marketing surveillance study reports, reports from other programs where data are being handled as solicited, and all clinical trial SAE reports using a targeted questionnaire / checklist. Expedited reporting to the EMA (see Section 2.2.1)	This item is appropriately communicated through current labeling: SPC Section 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use, and 5.2 Pharmacokinetic properties. Relevant preferred terms are included as ADRs in SPC Section 4.8 Undesirable effects.
Peripheral blood cytopenias	Routine pharmacovigilance activities including cumulative analysis in PSUR Targeted follow-up of all serious spontaneous reports, post-marketing surveillance study reports, reports from other programs where data are being handled as solicited, and all clinical trial SAE reports using a targeted questionnaire / checklist. Inclusion of monitoring of laboratory data in ongoing and planned clinical study protocols	This item is appropriately communicated through current labeling: SPC Section 4.4 Special warnings and precautions for use. Relevant preferred terms are included as ADRs in Section 4.8 Undesirable effects.
Compliance with posology and biological monitoring	Routine pharmacovigilance activities including cumulative analysis in PSUR.	SPC Section 4.2 Posology and method of administration and 4.4 Special warnings and precautions

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
	Investigation of compliance to risk minimization measures will be proposed.	for use. Additional risk minimization activities: Educational materials for physicians Effectiveness assessment: An investigation of compliance to risk minimization measures will be proposed.
Important identified interactions		
Interaction with food	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: SPC Sections 4.2 Posology and method of administration, 4.5 Interaction with other medicinal products and other forms of interaction and 5.2 Pharmacokinetic properties.
Interaction with aluminum-containing antacids	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: SPC Section 4.5 Interaction with other medicinal products and other forms of interaction.
Induction of CYP3A4 enzyme	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: SPC Section 4.5 Interaction with other medicinal products and other forms of interaction.
Inhibition of CYP1A2 enzyme	Routine pharmacovigilance activities	This item will be appropriately communicated through labeling: SPC Section 4.5 Interaction with other medicinal products and other forms of interaction.
Induction of UGT isoenzymes	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: SPC Section 4.5 Interaction with other medicinal products and other forms of interaction.
Inhibition of CYP2C8 enzyme	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: SPC Section 4.5 Interaction with other medicinal products and other forms of interaction.

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Interaction with cholestyramine	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: SPC Section 4.5 Interaction with other medicinal products and other forms of interaction and 5.2 (Pharmacokinetic properties (likely enterohepatic recycling).
Important missing information		
Pediatric use: pediatric patients age 2 to < 6 years	Routine pharmacovigilance activities including review in PSUR. Pediatric registry Study ICL670A2411. Study ICL670A2204 (including extension). Inclusion of monitoring of pediatric patients in ongoing and planned clinical study protocols.	SPC Section 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use, 5.1 Pharmacodynamic properties, and 5.2 Pharmacokinetic properties
Safety in pregnant women	Routine pharmacovigilance activities including review in PSUR.	This item is appropriately communicated through current labeling: SPC Section 4.6 Fertility, Pregnancy and lactation; and Section 5.3 Preclinical safety data.
Long-term exposure data in NTDT and safety in pediatric NTDT patients aged 10 to 17 years	Routine pharmacovigilance including a specific section for paediatric NTDT patients in the PSUR. Long-term exposure in NTDT: Routine pharmacovigilance. • 1-year Extension of study ICL670A2209. Paediatric NTDT patients aged 10 to 17 years: • Observational cohort study for paediatric NTDT patients over 10 years-old for whom deferoxamine is contraindicated or inadequate	This item is appropriately communicated through the proposed EU SPC, SPC Section 4.2 Posology and method of administration, 4.4 Warnings and precautions, and 5.1 Pharmacodynamic properties. .

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activity in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Observational cohort study for paediatric NTDT patients over 10 years-old for whom deferoxamine is contraindicated or inadequate	Final Study report: June 2021

Description	Due date
Investigation of compliance to risk minimization measures	Submission of proposal: 31 December 2012

The following updates to the additional risk minimisation activities were required:

The physician information for use of Exjade in patients with non-transfusion-dependent thalassaemia (NTDT) syndromes should contain the following key elements:

- Information that only one course of treatment is proposed for NTDT patients
- The recommended doses and the rules for starting treatment
- The rules for stopping when target liver iron concentration and serum ferritin are reached
- A warning to minimise the risk of over-chelation
- A warning on the necessity of closer monitoring of liver iron concentration and serum ferritin in the paediatric population
- A warning on the currently unknown safety consequences of long-term treatment in the paediatric population and the need to detect side effects

3. Benefit-Risk Balance

Benefits

Beneficial effects

Exjade is an efficient oral iron chelator already approved to reverse iron overload and maintain normal values in patients suffering from various transfusion dependent conditions. An iron chelating agent permit to achieve safe levels of body iron. This is a slow process because only a small proportion of body iron is available for chelation at any moment.

The pivotal study A2209 was a phase II randomised double blind placebo controlled study designed to assess the efficacy and the safety of deferasirox in NTDT patients (aged >10 years-old) with iron overload. One hundred and sixty-six (166) patients were included and followed during 52 weeks. The supportive study A2202 was designed to determine both safety and efficacy of deferasirox in a limited number of adult patients (49) with iron overload from hereditary hemochromatosis (HH). Study A2209 results showed a decrease in iron overload in patients with NTDT. The effect seems dose-dependent. On average, liver iron concentration decreased by 3.80 mg Fe/g dw in patients treated with EXJADE (starting dose 10 mg/kg/day) and increased by 0.38 mg Fe/g dw in patients treated with placebo ($p<0.001$). On average, serum ferritin decreased by 222.0 µg/l in patients treated with EXJADE (starting dose 10 mg/kg/day) and increased by 115 µg/l in patients treated with placebo ($p<0.001$).

Uncertainty in the knowledge about the beneficial effects.

There was no prospective challenge of any long-term treatment (with stopping rules after correction, maintenance recommendations and planned re-introduction of Exjade). Data showing that deferasirox was not only an active iron chelator, but can also be used a safe and efficient drug in NTDT patients on a long term ware thus lacking. No information is available on retreatment to correct a relapsed

overload. As a consequence, retreatment cannot be recommended as indicated in section 4.2 of the SmPC.

There was no direct comparison with deferoxamine, the current gold standard in secondary hemosiderosis, to demonstrate that inferior efficacy or safety can be

excluded. Thus, the use of Exjade in NTDT should be limited when deferoxamine therapy is contraindicated or inadequate.

Data in NTDT children are limited as only 21 paediatric patients were included in the study A2209 (with solely 13 patients in deferasirox groups). As a consequence, a warning has been included in section 4.4 of the SmPC to inform prescriber and highlight that paediatric patients should be closely monitored.

Risks

Unfavourable effects

Overall, the most frequent AEs (at least 10% in any deferasirox treatment group) in the NTDT patients (target population) were headache, upper respiratory tract infection, oropharyngeal pain, pyrexia, and rash. In general the safety profile can be considered as comparable to that one already described for the other approved indications.

The overall adverse event profile was consistent with the known safety profile of Exjade and complications of underlying conditions. Both studies (A2209 and A2202) provided in the context of this submission do not bring any new relevant information regarding the safety profile of Exjade. However, the number of paediatric patients (aged of 10-18 years-old) with NTDT was too low (n=13 in deferasirox groups) to draw any firm conclusion on the safety in this subpopulation.

Although no renal tubular damage were reported in the study population, the renal risk with Exjade is recognised and the mechanism of this risk is not yet fully understood.

As the planned duration of treatment in NTDT patients varies (more or less one year) depending of clinical features of the patients, of the renal risk in NTDT patients, with a long term exposure and especially in those patients in whom kidney function is often already compromised, should be carefully considered. It is difficult to assess whether renal toxicity can be manageable in these patients as the duration of treatment and dose tapering have not been addressed in the pivotal study. Indeed, deferasirox could be a long term treatment, and renal dysfunction is a severe factor of morbidity. The data provided do not allow affirming that there is a reversibility of the renal events associated with deferasirox use, after a drug interruption. As a consequence, retreatment cannot be recommended.

No new safety information related to hepatotoxicity have been reported; a close monitoring should be maintained in this population as per the current SmPC recommendation in section 4.4 of the SmPC.

Uncertainty in the knowledge about the unfavourable effects

Overchelation cannot be excluded in this population with moderate overload, especially when patients are exposed to 10mg/kg/day. Due to an increased potential risk of overchelation, a close monitoring of deferasirox treatment is warranted particularly in patients affected by HbE beta-thalassemia or alpha-thalassemia. The hypothesis of overchelation as a possible mechanism to explain the renal finding was considered interesting but not sufficient to explain the renal disorders associated with deferasirox. This

potential risk of overchelation could be addressed by the LIC and SF treatment stopping rules as well as the close monitoring and dosing recommendations as included in section 4.2 of the SmPC.

Further data are needed to address concerns on the ong term safety (particularly with respect to renal and hepatic toxicity) in paediatric patients, in view of the potential long term duration of therapy.As a consequence, risk minimisation measures concerning the paediatric population have been be strengthened.

Specifically for paediatric population, a warning for prescribers on the necessity of closer monitoring of LIC and SF and on the uncertainties of the safety consequences in the long term treatment should be include in the product information and risk minimization educational materials.

Furthermore, the MAH will conduct an observational study (cohort) withpaediatric NTDT patients over 10 years-old for whom deferoxamine is contra-indicated or inadequate in order to obtain long-term safety data from a significant sample of paediatic patients in real life. A specific section for paediatric NTDT patients in the future PSURs should also be provided.

Benefit-risk balance

Importance of favourable and unfavourable effects

Exjade is an efficient oral iron chelator already approved to reverse iron overload and maintain normal values in patients suffering from various transfusion dependent conditions. An iron chelating agent permit to achieve safe levels of body iron. This is a slow process because only a small proportion of body iron is available for chelation at any moment.

Study 2209 results (submitted in the context of the indication extension for NTDT patients over 10 years-old) show a decrease in iron overload in patients with NTDT. The effect seems dose-dependent. On average, liver iron concentration decreased by 3.80 mg Fe/g dw in patients treated with EXJADE (starting dose 10 mg/kg/day) and increased by 0.38 mg Fe/g dw in patients treated with placebo ($p<0.001$). On average, serum ferritin decreased by 222.0 µg/l in patients treated with EXJADE (starting dose 10 mg/kg/day) and increased by 115 µg/l in patients treated with placebo ($p<0.001$).

Overall, the most frequent AEs (at least 10% in any deferasirox treatment group) in the NTDT patients (target population) were headache, upper respiratory tract infection, oropharyngeal pain, pyrexia, and rash. In general the safety profile can be considered as comparable to that one already described for the other approved indications. The renal risk with Exjade has been recognised (renal risk mechanism is not yet fully understood).

However, as there was no comparison with the standard of care deferoxamine to demonstrate that loss of chance can be excluded (due to low efficacy or poor safety profile), the use of Exjade should be limited to NTDT patients *when deferoxamine therapy is contraindicated or inadequate.*

Furthermore, in view of the uncertainties of long-term use and lack of information on retreatment, the use of Exjade in these patients should be limited to a single course of treatment.

Finally, the long-term safety in paediatric patients needs to be closely monitored, through additional risk minimisation, PSURs and an observational cohort study.

Benefit-risk balance

Overall, the CHMP considered that the benefit-risk of Exjade in NTDT was positive in a restricted indication for patients aged 10 years and older when deferoxamine therapy is contraindicated or inadequate. The CHMP also considered that based on the data available, retreatment cannot be recommended.

Discussion on the benefit-risk balanceDue to the lack of comparison with deferoxamine (gold standard for secondary hemosiderosis) and so the potential loss of chance for these patients, the use of Exjade should in NTDT should be limited to patients *when deferoxamine therapy is contraindicated or inadequate.*

Due to uncertainties regarding long-term use and lack of information on retreatment with Exjade in NTDT patients, the use should be limited to only one single course of treatment. Also, to address the risk of potential overchelation, a close monitoring of efficacy parameters is needed, with SF to be evaluated monthlyand even in children where LIC should be assessed every 3 months when serum ferritin (SF) levels reach the limit of 800ng/ml.

Additionally, in order to ensure a narrow monitoring of the NTDT patients with thalassemia syndromes, recommended doses and starting/stopping rules when target LIC and SF are reached have been included in the product information as well as additional risk minimisation activities (i.e. educational materials).

Moreover, uncertainties remain concerning the long term use of Exjade, particularly in paediatric patients where data are very limited. As a consequence the long-term safety in paediatric patients needs to be closely monitored, through additional risk minimisation, PSURs (with a specific section on paediatric NTDT patients) and an observational cohort study.

Overall, the CHMP considered that the benefit-risk of Exjade in NTDT was positive in a restricted indication for patients aged 10 years and older when deferoxamine therapy is contraindicated or inadequate. The CHMP also considered that based on the data available, retreatment cannot be recommended.

4. Changes to the Product Information

The CHMP finally agreed to the following indication to be added in section 4.1 of the SmPC:

"EXJADE is also indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older."

In addition, consequently to this new indication, section 4.2 of the SmPC was updated with respect to the posology requirements in NTDT, a warning was added in section 4.4 due to the limited data in paediatric patients and need for close monitoring. Section 4.8 and 5.1 of the SmPC were also update with information on the clinical trials conducted in NTDT patients. The Package leaflet was updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s), which were reviewed and accepted by the CHMP.

User consultation with target patient groups on the package leaflet was submitted at the time of the initial marketing authorisation of Exjade. The MAH considered that no user consultation was required for this application as no significant changes were made to the package leaflet, which was accepted by the CHMP.

5. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

New indication of Exjade for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older. Consequently, sections 4.1, 4.2, 4.4, 4.8 and 5. of the SmPC and the package leaflet have been updated. Annex II has also been updated to include an obligation to conduct a post-authorisation measure. The Marketing Authorisation Holder also took the opportunity to update the product information with the latest QRD template (version 8.1).

The requested variation proposed amendments to: Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.

Other conditions and requirements of the marketing authorisation

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management plan

The MAH shall perform pharmacovigilance activities detailed in the Pharmacovigilance Plan as agreed in the RMP presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- when new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities,
- within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached,
- at the request of the European Medicines Agency.

PSURs

The MAH will continue to submit yearly PSURs until otherwise specified by the CHMP.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

The MAH shall set up a surveillance programme to collect information on the demographics of patients prescribed Exjade, any adverse reactions and reasons for discontinuation of Exjade. The formal protocols for the sentinel monitoring surveillance should be reviewed by the CHMP.

The MAH must inform the European Medicines Agency and the CHMP of the status and results of the surveillance programme in each Member State within 6 months of the Decision and at each update of the EU Risk Management Plan.

As well as the requirements in the legislation, the following serious ADRs should be forwarded on an expedited basis to the appropriate competent authority as well as summarised in the above reports:

- Increase in hepatic enzymes >10x ULN
- Serious rise in creatinine
- Results of renal biopsies, if available
- Cataracts
- Hearing loss
- Gallstones

The MAH must ensure that, at launch, all physicians who are expected to prescribe Exjade are provided with a physician information pack containing the following:

Product information

Physician information about Exjade (brochure and pocket card)

Patient information pack

The physician information about Exjade should contain the following key elements:

- The need to monitor serum ferritin monthly
- That Exjade causes rises in serum creatinine in some patients
    - The need to monitor serum creatinine
        - On two occasions prior to initiation of treatment
        - Every week during the first month of initiation of treatment or after therapy modification
        - Monthly thereafter
    - The need to reduce by 10 mg/kg the dose if serum creatinine rises:
        - Adults: >33% above baseline and creatinine clearance <LLN (90 ml/min)

- Paediatrics: either >ULN or creatinine clearance falls to <LLN at two consecutive visits.

- The need to interrupt treatment after a dose reduction if serum creatinine rises:
  - Adults and Paediatrics: remain >33% above baseline or creatinine clearance <LLN (90 ml/min)

- The need to consider renal biopsy:
  - When serum creatinine is elevated and if another abnormality has been detected (eg. proteinuria, signs of Fanconi's Syndrome).

- The importance of measuring creatinine clearance
- Brief overview of methods of measuring creatinine clearance
- That rises in serum transaminases occur in patients treated with Exjade
  - The need for liver function tests prior to prescription, then at monthly intervals or more often if clinically indicated
  - Not to prescribe to patients with pre-existing severe hepatic disease
  - The need to interrupt treatment if persistent and progressive increase in liver enzyme were noted.
- The need for annual auditory and ophthalmic testing

- The need for a guidance table highlighting pre-treatment measurements of serum creatinine, creatinine clearance, proteinuria, hepatic enzymes, ferritin, such as:

Before initiating treatment	
Serum creatinine at Day - X	Value 1
Serum creatinine at Day - Y	Value 2

X and Y are the days (to be determined) when pre-treatment measurements should be performed.

- That the safety database of Exjade is limited and physicians are encouraged to enrol patients in a surveillance programme (sentinel site monitoring and paediatric registry) to increase knowledge about the incidence of important ADRs.
  The information collected should include:
  - Anonymised patient details – age, sex, weight
  - Transfusion history and requirements
  - Initial dose of Exjade and subsequent changes in dose
  - Concomitant medications
  - Record of measurements of serum creatinine, creatinine clearance, proteinuria, hepatic enzymes, ferritin
  - Renal histology, if available
  - Reason for discontinuation
  - ADRs

- The educational programme should prompt doctors to report serious ADRs and certain selected ADRs as below:
  - All serious ADRs
  - Persistent and progressive increase in hepatic enzymes
  - Increase in serum creatinine levels (>33% above baseline) or clearance creatinine decrease (<90 ml/min)
  - Significant changes found in auditory or ophthalmological testing
  - Gallstones
  - Unexpected ADRs according to the SPC.

The Patient information pack should include the following information:

- Patient information leaflet
- Information on the need for regular monitoring, and when it should be carried out, of serum creatinine, creatinine clearance, proteinuria, hepatic enzymes, ferritin

- Information that renal biopsy may be considered if significant renal abnormalities occur
- Patient booklet where the physician can record the results of the above along with the dose of Exjade
- Reminder card for dates of tests

The physician information for use of Exjade in patients with non-transfusion-dependent thalassaemia (NTDT) syndromes should contain the following key elements:

- Information that only one course of treatment is proposed for NTDT patients
- The recommended doses and the rules for starting treatment
- The rules for stopping when target liver iron concentration and serum ferritin are reached
- A warning to minimise the risk of over-chelation
- A warning on the necessity of closer monitoring of liver iron concentration and serum ferritin in the paediatric population
- A warning on the currently unknown safety consequences of long-term treatment in the paediatric population and the need to detect side effects

Obligation to complete post-authorisation measures

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
The MAH shall conduct an observational cohort study in paediatric non-transfusion-dependent thalassaemia patients over 10 years old for whom deferoxamine is contraindicated or inadequate, in order to assess the long-term exposure and safety, based on a CHMP-agreed protocol.	June 2021 (final study report)

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

No amendments are required to the conditions for conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0216/2011 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.