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Human Medicines Evaluation Division

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

EXJADE

deferasirox

Procedure no: EMEA/H/C/000670/P46/070

Note

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

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1. Introduction

On 30 September 2016, the MAH submitted a completed paediatric study for Exjade, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study CICL670AIT14 "retrospective *data collection study to assess the long term renal safety of deferasirox in patients with transfusional hemosiderosis who were enrolled into the registration studies*" is a stand-alone study. This study is a retrospective chart review of patients from sites located in Italy who took part in the deferasirox registration studies (CICL670A0105,106,107,108 and 109) and were treated with at least one dose of DFX.

2.2. Information on the pharmaceutical formulation used in the study<ies>

Exjade is brand name for deferasirox presented as dispersible tablets in 3 doses strengths: 125, 250 and 500mg. The investigational drug was available as tablets at dosage strengths of 125 mg, 250 mg and 500 mg, packaged in high-density polyethylene (HDPE) bottles with an induction seal and child resistant closure.

2.3. Clinical aspects

2.3.1. Introduction

The orally active, tridentate iron chelator deferasirox (company research code: ICL670) is the active ingredient in Exjade® dispersible tablets. Exjade is currently approved in over 100 countries. In the European Union, it was approved on 28-Aug-2006 for the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older.

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

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

- in adult and paediatric patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells) aged 2 years and older,

- in adult and paediatric patients with other anaemias aged 2 years and older.

Since 20 December 2012, Exjade has been also indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with nontransfusion- dependent thalassaemia syndromes aged 10 years and older.

The MAH submitted the final report for this clinical study and a clinical overview of this study.

The MAH submitted a final report for

- study CICL670AIT14 " *retrospective data collection study to assess the long term renal safety of deferasirox in patients with transfusional hemosiderosis who were enrolled into the registration studies*"

2.3.2. Clinical study

Study CICL670AIT14 " retrospective data collection study to assess the long term renal safety of deferasirox in patients with transfusional hemosiderosis who were enrolled into the registration studies"

Description

This study is a retrospective chart review of patients from sites located in Italy who took part in the deferasirox registration studies (CICL670A0105,106,107,108 and 109) and were treated with at least one dose of DFX.

Methods

Objective(s)

Primary objective

The primary objective of this study was to evaluate the trend of serum creatinine over time in patients who were treated with at least one dose of deferasirox during registration studies CICL670A0105, A0106, A0107, A0108 and A0109.

Secondary objectives

The secondary objectives of the study were to evaluate:

- Renal function parameters over time in patients who had been treated with only deferasirox and no other chelators since enrollment in the registration studies.
- The frequency of renal adverse events from the time of completion/discontinuation of the registration study to the end of the retrospective study.
- The frequency of notable renal function parameters from the time of completion/discontinuation of the registration study to the end of the retrospective study.
- Renal function over time in patients who were on multiple chelators and other single chelators (deferoxamine, deferiprone, etc.) except deferasirox during the retrospective period.
- Renal function in patients who reported renal Adverse Events (AE) or confirmed notable renal laboratory values in the registration studies. Renal function in patients who reported renal AEs or confirmed notable renal laboratory values in the registration studies by underlying disease.

The exploratory objective of the study was to evaluate the role of serum ferritin levels and concomitant medications with known nephrotoxic effect on notable renal laboratory values and adverse events collected during retrospective data collection.

Study design

This was a retrospective chart review conducted at Italian investigational sites that enrolled transfusion-dependent patients in the deferasirox registration studies. Reviews were carried out on patients who were treated with deferasirox at least once during these studies. The first renal assessment in which serum creatinine, urinary protein and urinary creatinine values were available was collected for each quarter. The urinary protein/urinary creatinine ratio was collected directly from the patient chart if available or calculated using urinary protein and creatinine values. Data were retrospectively collected beginning from the time of completion of, or discontinuation from the registration studies until the patient assessment occurring at the site before enrollment. Written informed consent was provided giving permission for data to be included in this retrospective study.

Study population /Sample size

Patients who were treated with at least one dose of DFX during the registration studies and had renal function parameters available (below and above 18 years-old). The estimated sample size was 366 patients. The study enrolled 292 patients (80%) but due to screening failure in 10 patients, data for 282 patients were collected and analysed.

Inclusion criteria

1. Male or female subjects who had participated in deferasirox registration studies CICL670A0105, A0106, A0107, A0108 or A0109. Some patients were still aged below 18 years at the time of enrollment.

2. Treatment with at least one dose of deferasirox while enrolled in one of the above - mentioned deferasirox registration studies/their extensions.

3. At least one post-baseline serum creatinine value from participation in the registration studies.

4. Available medical records after discontinuation from registration studies.

5. Written informed consent provided prior to any screening procedure.

Exclusion criteria

None

Treatments

In the registration studies, the investigational study drug used in the course of this study was deferasirox (ICL670). This study did not require a specific ongoing treatment; patients may have been treated with iron chelators or any other medication at the Investigator's discretion and according to local prescribing information.

All iron chelation therapy administered during the retrospective study, along with the corresponding dose and duration were recorded. All medications and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the observation period were recorded on the Case Report Form (CRF).

CHMP comment

Patients enrolled in the registration studies (and receiving at least one dose of deferasirox) are followed during retrospective period but can be treated with either other iron chelators (mono of multiple therapies) or any other medications at the investigator's discretion. Therefore, the long term renal safety of deferasirox will be difficult to assess based on these data, especially as only 5 patients have been treated with deferasirox during the retrospective period.

Outcomes/endpoints

The purpose of this study was to assess the long-term renal safety of deferasirox in patients with transfusional hemosiderosis. Renal adverse events and renal laboratory parameters were collected on a quarterly basis. The primary variable was serum creatinine (SCr). SCr, urinary protein and creatinine, urinary protein/creatinine ratio, creatinine clearance (if available), hemoglobin levels and serum ferritin were collected quarterly during the retrospective period.

The endpoints were the trends in renal parameters serum creatinine, urine protein and urine protein/creatinine ratio (UPCR) over time, starting from baseline value of the registration studies, worst value in the registration studies (data from the registration studies were already available) and then values collected quarterly in the retrospective study. The primary variable was serum creatinine. Renal adverse events and abnormal laboratory values were collected also.

Statistical Methods

All statistical analyses were produced using SAS® release 9.4 or later (SAS Institute Inc., Cary NC, USA).

No formal statistical hypothesis was stated and therefore all the analyses are descriptive.

All analyses were performed on the Safety Set.

Results

Recruitment/ Number analysed

Two hundred ninety-two patients (292) were enrolled in the study and 282 patients were evaluated (10 were screening failures). Sixty-five (23.05%) patients were aged <18 years at Quarter 1 of data collection.

More than 90% of both the total population and pediatric population were observed for at least seven years following the completion of/discontinuation from the previous registration trials. The percentage of patients observed after the seventh year decreases progressively until Q1 of year 13, when data was collected for only one patient.

Patient exposure

Table 10-6 Exposure to Deferasirox overall and by period (Safety Set)

		Age <18 years	Age ≥ 18 years	Total
		(N=65)	(N=217)	(N=282)
Treatment duration (years)	N	65	217	282
	Mean	8.72	7.63	7.88
	Std. Dev	4.18	4.26	4.25
	25th Percentile	4.68	3.61	3.81
	Median	10.85	8.18	9.42
	75th Percentile	11.99	11.68	11.79
	Min	0.03	0.08	0.03
	Max	12.94	14.14	14.14

		Age <18 years		Age ≥ 18 years		Total	
		Registration period	Retrospective period	Registration period	Retrospective period	Registration period	Retrospective period
		(N=65)	(N=53)	(N=217)	(N=162)	(N=282)	(N=215)
Treatment duration (years)	N	65	53	217	162	282	215
	Mean	3.57	6.56	3.42	5.96	3.45	6.11
	Std. Dev	1.46	2.27	1.63	3.00	1.59	2.84
	25th Percentile	2.30	6.43	2.08	4.00	2.11	4.45
	Median	3.92	7.25	3.71	7.12	3.75	7.15
	75th Percentile	4.76	7.50	4.70	7.58	4.74	7.56
	Min	0.03	0.07	0.02	0.00	0.02	0.00
	Max	5.41	12.66	6.36	13.36	6.36	13.36

		Age <18 years		Age ≥ 18 years		Total	
		(N=65)		(N=217)		(N=282)	
		N	%	N	%	N	%
Years of exposure	At least 1 year	61	93.85	206	94.93	267	94.68
	At least 2 years	58	89.23	193	88.94	251	89.01
	At least 3 years	54	83.08	172	79.26	226	80.14
	At least 4 years	53	81.54	156	71.89	209	74.11
	At least 5 years	47	72.31	137	63.13	184	65.25
	At least 6 years	46	70.77	130	59.91	176	62.41
	At least 7 years	44	67.69	119	54.84	163	57.80
	At least 8 years	43	66.15	110	50.69	153	54.26
	At least 9 years	42	64.62	103	47.47	145	51.42
	At least 10 years	40	61.54	93	42.86	133	47.16
	At least 11 years	30	46.15	75	34.56	105	37.23
	At least 12 years	16	24.62	41	18.89	57	20.21
	At least 13 years	0	0.00	12	5.53	12	4.26
	At least 14 years	0	0.00	3	1.38	3	1.06

		Age <18 years				Age ≥ 18 years				Total			
		Registration period		Retrospective period		Registration period		Retrospective period		Registration period		Retrospective period	
		(N = 65)		(N = 53)		(N = 217)		(N = 162)		(N = 282)		(N = 215)	
		N	%	N	%	N	%	N	%	N	%	N	%
Years of exposure	At least 1 year	60	92.31	51	96.23	193	88.94	146	90.12	253	89.72	197	91.63
	At least 2 years	54	83.08	49	92.45	167	76.96	140	86.42	221	78.37	189	87.91
	At least 3 years	45	69.23	48	90.57	140	64.52	127	78.40	185	65.60	175	81.40
	At least 4 years	31	47.69	46	86.79	86	39.63	122	75.31	117	41.49	168	78.14
	At least 5 years	2	3.08	43	81.13	28	12.90	109	67.28	30	10.64	152	70.70
	At least 6 years	0	0	41	77.36	10	4.61	101	62.35	10	3.55	142	66.05
	At least 7 years	0	0	33	62.26	0	0	87	53.70	0	0	120	55.81
	At least 8 years	0	0	3	5.66	0	0	18	11.11	0	0	21	9.77
	At least 9 years	0	0	3	5.66	0	0	13	8.02	0	0	16	7.44
	At least 10 years	0	0	3	5.66	0	0	9	5.56	0	0	12	5.58
	At least 11 years	0	0	1	1.89	0	0	7	4.32	0	0	8	3.72
	At least 12 years	0	0	1	1.89	0	0	5	3.09	0	0	6	2.79
	At least 13 years	0	0	0	0.00	0	0	2	1.23	0	0	2	0.93
Source: Table 14.3-1.1													

All 282 patients of the Safety Set took at least one dose of deferasirox in the registration period and 215 took at least one dose in the retrospective period.

Treatment duration in the safety set, calculated as the time in years elapsed from the date of the first dose of deferasirox until the date of the last dose was equal to 3.45 ± 1.59 years (range 0.02 – 6.36

years) in the registration period and 6.11 ± 2.84 years (range 0.002 – 13.36 years) in the retrospective period.

In patients under 18 years of age (at Q1), treatment exposure was equal to 3.57 ± 1.46 years (range 0.03 – 5.41 years) in the registration period and 6.56 ±2.27 years (range 0.07 – 12.66 years) in the retrospective period.

In patients 18 or over, treatment exposure was equal to 3.42 ± 1.63 years (range 0.02 – 6.36 years) and 5.96 ± 3.00 years (range 0.00 – 13.36 years) in the registration and retrospective periods respectively.

Overall, treatment duration was 7.88 ± 4.25 years (range 0.03 – 14.14 years) in the safety set, 8.72 ± 4.18 years (range 0.03 – 12.94 years) in patients under 18 years of age and 7.63 ± 4.26 years (range 0.08 – 14.14 years) in patients 18 or over. (Note: overall treatment duration was calculated excluding the time period elapsed between the last dose of deferasirox in the registration trials and the first dose of deferasirox in the retrospective trial. Temporary interruptions in treatment during the registration and retrospective periods were not excluded from the calculation).

The recommended initial daily dose of dispersible tablet is 20 mg/kg body weight. In the safety set, average daily dose was in mean 1,032.19 ± 438.77 mg with a range between 166.86 and 2,810.13 mg in the registration period and 1,385.59 ± 499.98 mg (ranging between 215.18 and 2,629.94 mg) in the retrospective period.

In the under 18 population, average daily dose was in mean 697.80 ± 326.46 mg (range 191.36 – 1635.44 mg) and 1,214.86 ± 420.69 mg (range 279.74 – 2,236.22 mg) in the registration period and retrospective period respectively.

In patients over 18, average daily dose was in mean 1,132.35 ± 418.51 mg (range 166.86 – 2,810.13 mg) in the registration period and 1,441.79 ± 512.28 mg (range 215.18 – 2,629.94 mg) in the retrospective period.

CHMP comment

It will be difficult to analyse the renal safety profile compared with the treatment duration based on the data provided by the MAH: indeed, the methodology used was not detailed enough by the MAH. For instance, the MAH did not discuss why temporary interruptions in treatment during the registration and retrospective periods were not excluded from the calculation. The MAH should provide a clear justification of the methodology used for the treatment duration calculation with the reason why temporary interruptions in treatment during the registration and retrospective periods were not excluded from the calculation and should provide an accurate estimation of the treatment duration with deferasirox (in patient-year) for the safety set (respectively for adults and paediatric patients).

Table 10-7 Deferasirox average dose (Safety Set)

		Age <18 years		Age ≥ 18 years		Total	
		Registration period	Retrospective period	Registration period	Retrospective period	Registration period	Retrospective period
		(N=65)	(N=53)	(N=217)	(N=162)	(N=282)	(N=215)
Average dose (mg)	N	65	53	217	161	282	214
	Mean	697.80	1214.86	1132.35	1441.79	1032.19	1385.59
	Std. Dev	326.46	420.69	418.51	512.28	438.77	499.98
	25th Percentile	442.63	955.71	856.29	1080.54	750.28	1056.03
	Median	705.18	1215.11	1089.51	1467.25	995.19	1385.04
	75th Percentile	891.68	1500.00	1377.38	1800.13	1296.21	1729.65
	Min	191.36	279.74	166.86	215.18	166.86	215.18
	Max	1635.44	2236.22	2810.13	2629.94	2810.13	2629.94

The average dose in mg was calculated as the total dose divided by the treatment duration in days.
Source: Table 14.3-1.1

During the retrospective period, 179 patients (63.48% of the Safety Set) took at least one other iron-chelating therapy. Thirty-eight (38) of these patients were under the age of 18 (58.46% of the <18 population). The most common chelating agents were deferoxamine (reported by 56.03% of the patients of the Safety Set) and deferiprone (reported by 48.23% of the patients of the Safety Set). The other chelators were in most cases given sequentially, but in some cases concomitantly with deferasirox.

CHMP comment

A majority of patients (63%) followed during the retrospective period have been treated with other iron chelators (in mono or multiple therapies). Therefore, the long term renal safety of deferasirox will be difficult to assess based on these data. A safety subgroup (N°1) included all patients receiving only deferasirox have been analyzed: unfortunately, only 5 patients were included in this subgroup and no conclusion can be drawn.

Baseline data

Patient distribution according to participation in the previous registration trials is shown in Table 5-1. Most patients (63.08% of patients < 18 years of age and 49.77% of patients ≥ 18) participated in study CICL670A0107/E.

Table 5-1 Analysis population according to participation in registration studies (Safety set)

		Age < 18 years (N = 65)		Age ≥ 18 years (N = 217)		Total (N = 282)	
		N	%	N	%	N	%
Previous Registration Study	CICL670A0105/E1/E2	0	0.00	60	27.65	60	21.28
	CICL670A0106/E	19	29.23	12	5.53	31	10.99
	CICL670A0107/E	41	63.08	108	49.77	149	52.84
	CICL670A0108/E	4	6.15	31	14.29	35	12.41
	CICL670A0109/E	1	1.54	6	2.76	7	2.48

Demographic data by age group are shown in Table 5-2.

Table 5-2 Demographic data (safety set)

		Age <18 years (N = 65)	Age ≥ 18 years (N = 217)	Total (N = 282)
Age at Screening of Registration Studies (years)	Mean (SD)	8.94 (3.18)	25.71 (11.36)	21.85 (12.31)
	25th Percentile	6.00	18.00	13.00
	Median	10.00	24.00	21.00
	75th Percentile	11.00	29.00	28.00
	Range	2-16	12-81	2-81
Age at First Quarter (years)	Mean (SD)	13.15 (3.17)	29.86 (10.95)	26.01(12.01)
	25th Percentile	11.00	23.00	18.00
	Median	14.00	28.00	25.00
	75th Percentile	16.00	34.00	31.00
	Range	6-17	18-86	6-86
Gender	Male	29	87	116
	Female	36	130	166

Source: [Study ICL670AIT14- Table 14.1-5]

Medical history was obtained from data collected during the registration studies. Almost all the patients (92.31% of patients <18 years and 98.16% of those ≥ 18 years at Q1) reported at least one relevant condition. Congenital, familial and genetic disorders (75.38% in < 18 and 63.59% in ≥ 18), metabolism and nutrition disorders (61.54% and 48.39%), endocrine disorders (9.23% and 47%) and musculoskeletal and connective tissue disorders (9.23% and 41.94%) were the most frequent ongoing System Organ Classes (SOC) affecting patients in both age groups at the start of the registration studies.

Efficacy results

Efficacy was not assessed in the study CICL670AIT14.

Safety results

The primary objective was to evaluate the trend of SCr over time in patients who were treated with at least one dose of deferasirox during registration studies CICL670A0105, 106, 107, 108 and 109.

Evaluation

Of the safety set defined as all consenting patients at the sites in Italy who received at least one dose of Exjade in registration studies 105, 106, 107, 108 and 109 and their extensions), the following Safety Set subgroups were defined:

☐ Subgroup 1: Patients treated with deferasirox only and no other chelators since enrollment in the registration studies.

☐ Subgroup 2: Patients on multiple chelators and other single chelators (deferoxamine, deferiprone, etc.) except deferasirox during the retrospective period.

☐ Subgroup 3: Patients who reported renal AEs or confirmed notable renal laboratory values in the registration studies.

☐ Subgroup 4: Patients who reported renal AEs or confirmed notable renal laboratory values during the retrospective period.

All the analyses were performed on the Safety Set.

Table 10-3 Analysis population according to subgroup (Safety set)

		Age <18 years (N=65)		Age ≥ 18 years (N=217)		Total (N=282)	
		N	%	N	%	N	%
Analysis Population	Safety set	65	100	217	100	282	100
	Safety set - Subgroup 1	1	1.54	4	1.84	5	1.77
	Safety set - Subgroup 2	12	18.46	50	23.04	62	21.99
	Safety set - Subgroup 3	43	66.15	154	70.97	197	69.86
	Safety set - Subgroup 4	33	50.77	132	60.83	165	58.51
Source: Table 14.1-3							

The following variables were collected quarterly:

☐ Serum creatinine

☐ Urinary protein

☐ Urinary creatinine

☐ Urinary protein/creatinine ratio

☐ Creatinine clearance (if available)

☐ Hemoglobin levels

☐ Serum ferritin

Renal Adverse Events and abnormal renal laboratory values or test results were also collected.

Adverse events

1- Subgroup analysis

Safety set- Subgroup 1

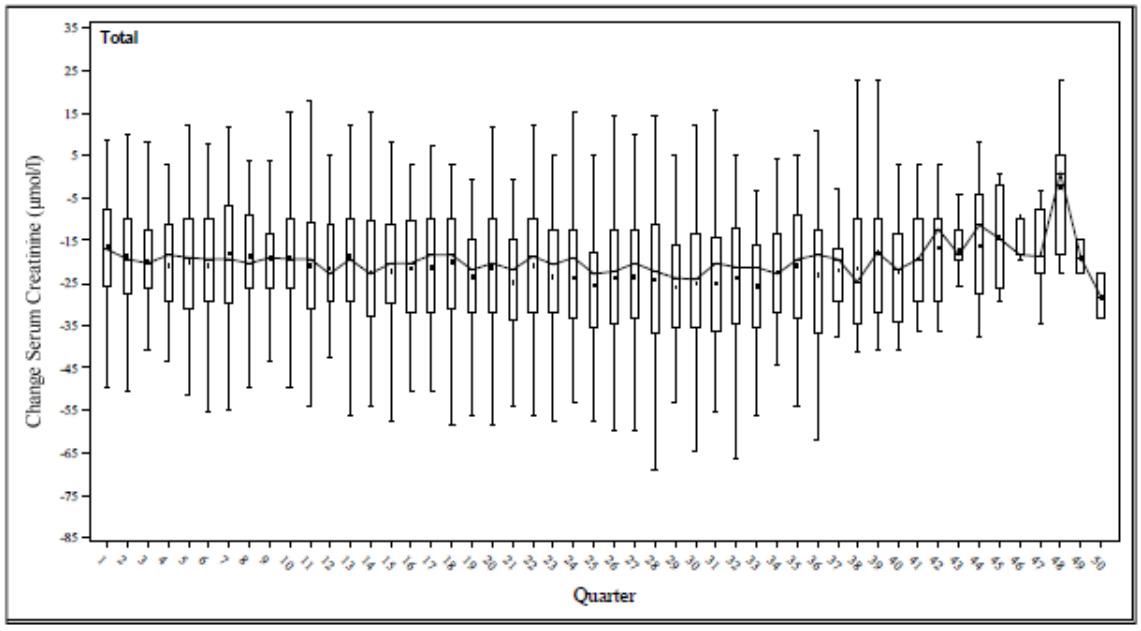
No meaningful analysis could be performed since only five patients were treated with only deferasirox and no other chelators since enrollment in the registration studies.

CHMP comment
One of the 2nd objectives is to evaluate renal function parameters over time in patients who had been treated with only deferasirox and no other chelators since enrollment in the registration studies (subgroup 1). However, this 2nd objective is not reached as only few patients (only 5) were classified in subgroup 1 and no comprehensive analysis was performed.

Safety set- Subgroup 2

Subgroup 2 (N=62) was made up of all patients who did not take deferasirox during the retrospective period. These patients were on multiple chelators (sequentially or in combination) or other single chelators (deferoxamine, deferiprone, etc.) other than deferasirox during the retrospective period.

Figure 5-1 Changes vs worst value of serum creatinine by visit (Safety Set – Subgroup 2)



Source: [Study ICL670AIT14- Figure 14.3-2.7]

The mean changes in SCr vs. worst value of the registration studies were again quite stable during the retrospective period and fluctuated between -15 and -25 (µmol/l). No conclusions can be drawn from the comparison of the two age groups given their small size (12 patients under 18 years). Nevertheless, younger patients did have lower mean values in comparison with patients aged 18 years or older during the first quarters of collection.

CHMP comment

One of the 2nd objectives is to evaluate renal function over time in patients who were on multiple chelators and other single chelators (deferoxamine, deferiprone, etc.) except deferasirox during the retrospective period. It seems that no deterioration of renal function during the retrospective period was noted with therapies other than deferasirox in this safety subgroup N°2 as the mean changes in SCr is relatively stable.

However, the MAH did not provide the justification for having chosen mean change vs worst value instead of baseline value. This should be done and detailed interpretation should be provided.

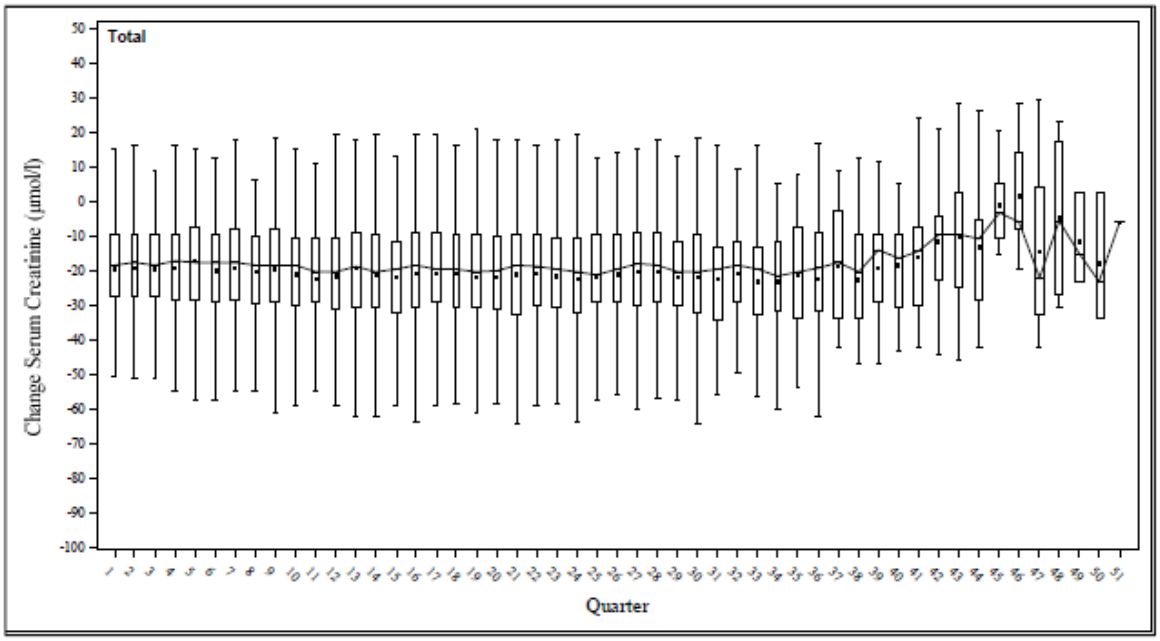
However, instead of having the mean change in absolute value vs worst value, it would have been more appropriate to have the percentage of SCr change compared to baseline at registration enrollment for each quarter. This should be done also for CrCl changes.

No significative difference between paediatric population and total population has been identified.

Safety set-Subgroup 3

Safety Set – Subgroup 3 (N=197) comprised of patients with renal AEs or confirmed notable renal laboratory values in the registration studies. Forty-three were less than 18 years of age at Q1 (66.15% of the <18 population).

Figure 5-3 Changes vs worst value of serum creatinine by visit (Safety Set – Subgroup 3)



Source: [Study ICL670AIT14- Figure 14.3-2.9]

Mean SCr at baseline of the registration studies for the safety set was 53.23 ± 13.72 µmol/l (range 26.10 – 87.96 µmol/l) while the mean worst value collected was equal to 82.95 ± 21.11 µmol/l (range 41.50 – 156.50 µmol/l). In patients < 18 years, baseline and worst values were 40.10 ± 7.84 µmol/l (range 26.10 – 62.32 µmol/l) and 67.16 ± 13.67 µmol/l (range 41.50 – 107.80 µmol/l) respectively.

As in the full safety set, mean/median values were higher than baseline value but lower than worst value. The mean/median values were slightly higher than values of the Safety Set (around 62 µmol/l in mean vs. 60 µmol/l in mean) and remained stable until Quarter 43, when only 11 patients (2 less than 18 years of age) were still under observation and mean/median values started to fluctuate. Mean values in patients ≥ 18 years were consistently higher, but similar to those reported for patients < 18 years of age.

CHMP comment

One of the 2nd objectives is to evaluate renal function in patients who reported renal Adverse Events (AE) or confirmed notable renal laboratory values in the registration studies. A description of renal function in patients who reported renal AEs or confirmed notable renal laboratory values in the registration studies by underlying disease was also made. Almost all patients had beta-thalassemia.

Similarly, it seems that no deterioration of renal function was noted in this safety subgroup N°3 as the mean changes in SCr is relatively stable. However, instead of having the mean change in absolute value vs worst value, it would have been more appropriate to have the percentage of SCr change compared to baseline at registration enrollment. No significative difference between paediatric population and total population has been identified.

In addition, the interpretation of these data is difficult as of these 197 patients, we do not known the percentage of patients taking deferasirox (monotherapy / sequential / concomitant) during the retrospective period. The MAH should clarify and discuss if any renal deterioration is observed in each subgroup taking deferasirox (monotherapy / sequential / concomitant) compared with baseline.

Safety set- Subgroup 4

Subgroup 4 (N=165) comprised of patients with renal AEs or confirmed notable renal laboratory values during the retrospective period.

A notable value for serum creatinine was defined as an increase ≥ 33% from baseline and > upper normal limit at two consecutive measurements at least 7 days apart (for this reason the parameter does not apply to Q1). Very few adult patients (1-3 per quarter) presented notable values and only one notable value was collected for patients <18 years of age (Q28).

One to 15 patients per quarter had a notable urinary protein value (≥ 300 mg/day).

A notable urinary protein/creatinine ratio was defined as one ≥ 1.0. The very few values available were almost all normal.

Finally, it is worth pointing out that many of the clinically notable laboratory values occurred concomitantly with the use of medications with potentially nephrotoxic effects.

CHMP comment

Of the 165 patients included in subgroup 4, no patient experienced acute renal failure or end stage renal disease. A total of 87 patients (52.41% of subgroup 4) were affected by renal AEs in the retrospective period including 18 paediatric patients (<18 years-old). No details were provided on the nature of renal AEs in this subgroup. In addition a discrepancy was noted with table 14.3.1-6 where a total of 86 patients experienced renal AE (52.12%). *The MAH should clarify.*

One of the 2nd objectives is to evaluate the frequency of renal adverse events and notable renal function parameters from the time of completion/discontinuation of the registration study to end of the retrospective study.

It would be appreciated that the MAH performed a comprehensive safety analysis in this subgroup n°4 with a description of renal AEs and notable renal function parameters by type of patients (i.e patients on deferasirox only, on multiple chelators (by different combinations), other single chelators (deferoxamine, deferiprone).

2- <u>Renal adverse events</u>

A summary of patients who experienced one or more renal adverse events during the retrospective period is presented in Table 5-3.

Renal AEs were reported in 30.50% of the overall safety set, in 26.15% of the patients under 18 years of age and in 31.80% of those 18 or older. The total number of renal AEs was however much higher in patients aged 18 or older than in patients under 18 years of age (164 vs. 40 for total renal AEs and 110 vs. 27 for renal AEs respectively).

Eight patients (2.84%) had at least one serious renal AE (7 in group " ≥ 18 years" and 1 in group "<18 years"), seven (2.48%) had a renal AE of severe intensity (6 in group "≥ 18 years" and 1 in group "<18 years"), 5 (1.77%) discontinued treatment with deferasirox due to renal AE (all in group "≥ 18 years") and 33 patients (11.70%) had at least one renal AE suspected of being related to deferasirox.

Table 5-3 Summary of patients with renal adverse events (safety set)

	Age < 18 years (N = 65)		Age ≥ 18 years (N = 217)		Total (N = 282)	
	N	%	N	%	N	%
Number of Renal Adverse Events	40	-	164	-	204	-
Number of distinct Renal Adverse Events by Low Level Term	27	-	110	-	137	-
Patients with Renal Adverse Events	17	26.15	69	31.80	86	30.50
Patients with Serious Renal Adverse Events	1	1.54	7	3.23	8	2.84
Patients with Severe Renal Adverse Events	1	1.54	6	2.76	7	2.48
Patients with Suspected Exjade-related Renal Adverse Events	10	15.38	23	10.60	33	11.70
Patients with Renal Adverse Events leading to Exjade discontinuation	0	0.00	5	2.30	5	1.77

Source: [Study ICL670AIT14- Table 14.3-1.1]

The most common AEs were **nephrolithiasis** in both age groups (11.52% of patients aged 18 or older and 9.23% of patients under 18 years of age), **renal colics,** especially among patients aged 18 or older (11.52 % in group "≥ 18 years" and 4.62% in group "< 18 years"), followed by **abnormal/increased urine protein/creatinine ratios, abnormal/increased blood creatinine, and proteinuria.**

<u>Serious renal AEs</u>

Eight patients (2.84% of Safety Set) had serious renal adverse events, only one under the age of 18 at Q1 (Patient 02_020), had at least one serious renal adverse event. No causal relationship was suspected between these SAEs and treatment with deferasirox.

Table 10-14 Serious renal adverse events by SOC and PT (safety set)

			Age <18 years (N=65)		Age ≥ 18 years (N=217)		Total (N=282)	
			N	%	N	%	N	%
	System Organ Class	Preferred Term	1	1.54	7	3.23	8	2.84
Patients with Serious renal AEs								
Patients with serious renal AEs by SOC and PT	Investigations	-TOTAL by SOC-	0	0	1	0.46	1	0.35
		Blood creatinine increased	0	0	1	0.46	1	0.35
	Renal and urinary disorders	-TOTAL by SOC-	1	1.54	6	2.76	7	2.48
		Acute kidney injury	0	0	1	0.46	1	0.35
		Hematuria	1	1.54	0	0	1	0.35
		Hydronephrosis	0	0	1	0.46	1	0.35
		Nephrolithiasis	0	0	2	0.92	2	0.71
		Renal colic	0	0	2	0.92	2	0.71
		Renal failure	0	0	1	0.46	1	0.35
		Urethral stenosis	0	0	1	0.46	1	0.35

AEs=Adverse events, SOC=System Organ Class, PT=Preferred term
A patient could report more than one serious renal AE. Patients were counted only once in each row.
Only serious renal AEs reported in the retrospective period were considered.
Terms were codified with MedDRA dictionary, version 18.1.
Source: Table 14.3.1-3

Brief narratives of the serious adverse events occurred during the retrospective period are provided as follows.

- Patient, underlying condition: beta thalassemia, SAE: **acute kidney injury**.

the 1st date on her chart review after participation in study CICL670A0107/E was 17 August 2008. , the patient was hospitalized for acute **kidney injury occurring during the course of acute pancreatitis**. Deferasirox, which the patient had been taking regularly during the retrospective period, was temporarily interrupted while she was being treated. The event was considered resolved on 22 August 2012. The event was not suspected of being related to deferasirox and did not reoccur.

- Patient, underlying condition: beta thalassemia, SAE: **hematuria.**

the first date on his chart review after participation in study CICL670A0107/E was 27 August 2008. , the patient was hospitalized for hematuria. Deferasirox was temporarily interrupted. The event was considered resolved the following day and no causal relationship was suspected between the event and deferasirox. Hematuria reoccurred almost 2 years later but was not serious, was not suspected and did not require any action.

- Patient, underlying condition: beta thalassemia, SAE: **nephrolithiasis**.

the first date on his chart review after participation in study CICL670A0106/E was 8 March 2008. The patient presented nephrolithiasis starting on "16 September 2009,", and was hospitalized. The patient had used deferoxamine from December 2007 to December 2012 and deferasirox from December 2012 to February 2013. Deferasirox was permanently discontinued in February 2013 due to proteinuria with

subsequent restart of deferoxamine. Nephrolithiasis was not suspected of being related to treatment. The event was considered resolved on 12 March 2014.

- Patient, underlying condition: beta thalassemia, SAE: **urethral stenosis** (two occurrences).

the first date on his chart review after participation in study CICL670A0105/E1/E2 was 14 June 2006. The patient used deferoxamine or deferiprone but not deferasirox as iron chelator during the retrospective period. He was hospitalized twice) due to urethral stenosis of severe intensity.

- Patient, underlying condition: beta thalassemia, SAE**: nephrolithiasis**.

the first date on her chart review after participation in study CICL670A0105/E1/E2 was 21 April 2003. The patient used deferoxamine or deferiprone but not deferasirox as chelation therapy during the retrospective period. On 17 March 2003, , the patient was diagnosed with nephrolithiasis and was hospitalized for extracorporeal lithotripsy. The event was considered resolved on 9 June 2003.

- Patient, underlying condition: beta thalassemia, SAE: **renal colic**.

the first date on his chart review after participation in study CICL670A0108/E was 7 August 2008. On 5 November 2013, , the patient was diagnosed as having renal colics, which were treated and resolved on the same day. No action was taken concerning the study drug (deferasirox) and no causal relationship was suspected between study drug and event.

- Patient, underlying condition: MDS, SAE: **blood creatinine increased.**

the first date on his chart review after participation in study CICL670A0108/E was 14 October 2004. No iron chelators were used by this patient during the retrospective period. The patient was hospitalized due to an increase of creatinine above the upper limit of normal. The event was then considered resolved on 22 April 2005.

- Patient, underlying condition: beta thalassemia, SAEs: **left kidney failure, right renal colic, right hydronephrosis**.

the first date on her chart review after participation in study CICL670A0107/E was 4 January 2007. The patient used deferoxamine or deferiprone but not deferasirox as iron chelator during the retrospective period. , the patient was hospitalized due to hydronephrosis and colic of the right kidney along with anuria. She was discharged from the hospital two weeks later on 16 January. On 31 March 2011, the patient was diagnosed with renal failure. She was hospitalized for a nephrectomy of the left kidney, which was found to be atrophic (in 2007, the patient had been diagnosed with "massive nephrolithiasis of the left kidney").

Renal AEs suspected to be related to deferasirox

Thirty-three patients (11.70% of the Safety Set) were affected by renal adverse events suspected of being related to treatment with deferasirox. Ten of these patients were under the age of 18 years at Q1 (15.38% of the patients <18)

(A summary of these AEs is provided by System Organ Class and Preferred Term in Table 10-15.

Table 10-15 Renal adverse events suspected of being deferasirox-related by SOC and PT (Safety Set)

			Age <18 years (N=65)		Age ≥ 18 years (N=217)		Total (N=282)	
			N	%	N	%	N	%
	System Organ Class	**Preferred Term**	10	15.38	23	10.60	33	11.70
Patients with suspected deferasirox -related renal AEs								
Patients with suspected deferasirox -related renal AEs by SOC and PT	Investigations	-TOTAL by SOC-	8	12.31	14	6.45	22	7.80
		Blood creatinine increased	2	3.08	6	2.76	8	2.84
		Protein urine present	0	0	2	0.92	2	0.71
		Urine protein/creatinine ratio abnormal	5	7.69	6	2.76	11	3.90
		Urine protein/creatinine ratio increased	1	1.54	2	0.92	3	1.06
	Renal and urinary disorders	-TOTAL by SOC-	4	6.15	11	5.07	15	5.32
		Calculus ureteric	0	0.00	1	0.46	1	0.35
		Glycosuria	0	0.00	2	0.92	2	0.71
		Nephrocalcinosis	1	1.54	0	0	1	0.35
		Proteinuria	2	3.08	7	3.23	9	3.19
		Renal colic	1	1.54	0	0	1	0.35
		Renal glycosuria	0	0	1	0.46	1	0.35
		Renal tubular disorder	0	0	1	0.46	1	0.35
	Surgical and medical procedures	-TOTAL by SOC-	1	1.54	0	0	1	0.35
		Lithotripsy	1	1.54	0	0	1	0.35

AEs=Adverse events, SOC=System Organ Class, PT=Preferred term
A patient could report more than one renal AE. Patients were counted only once in each row.
Only renal AEs reported in the retrospective period were considered.
Terms were codified with MedDRA dictionary, version 18.1.
Source: Table 14.3.1-4

Proteinuria (3.08% and 3.23%), abnormal/increased urine protein/creatinine ratio (9.23% and 3.69%) and blood creatinine increased (3.08% and 2.76%) were the most frequently reported events in both patients under 18 years of age and patients aged 18 or older respectively. None of these events was serious and four were considered of severe intensity: patient presented a severe increase of urine protein/creatinine ratio, patient presented a severe increase of urine protein/creatinine ratio and proteinuria, and patient was affected by severe glycosuria. In most cases, deferasirox was temporarily interrupted or dosage was adjusted and no further action was required.

Renal AEs leading to drug discontinuation

Five patients (1.77%), all aged 18 years or older, did however discontinue treatment with deferasirox permanently due to renal adverse events. No patients under the age of 18 years permanently discontinued treatment due to renal adverse events.

Table 10-16 Renal adverse events causing permanent discontinuation of deferasirox by SOC and PT (Safety Set)

			Age <18 years		Age ≥ 18 years		Total	
			(N=65)		(N=217)		(N=282)	
			N	%	N	%	N	%
	System Organ Class	**Preferred Term**						
Patients with renal AEs leading to permanently discontinuation of deferasirox			0	0	5	2.30	5	1.77
Patients with renal AEs leading to permanently discontinuation of deferasirox by SOC and PT	Investigations	-TOTAL by SOC-	0	0	2	0.92	2	0.71
		Blood creatinine increased	0	0	2	0.92	2	0.71
	Renal and urinary disorders	-TOTAL by SOC-	0	0	3	1.38	3	1.06
		Glycosuria	0	0	1	0.46	1	0.35
		Proteinuria	0	0	1	0.46	1	0.35
		Renal glycosuria	0	0	1	0.46	1	0.35

AEs=Adverse events, SOC=System Organ Class, PT=Preferred term
A patient could report more than one Renal Adverse Event. Patients were counted only once in each row.
Only Renal Adverse Events reported in the retrospective period were considered.
Terms were codified with MedDRA dictionary, version 18.1.
Source: Table 14.3.1-5

Eighty-seven patients (52.41% of Subgroup 4) were affected by renal adverse events in the retrospective period. Eighteen of these patients were under the age of 18 years (52.94% of Subgroup 4 < 18 years).

Table 10-17 Renal adverse events, acute renal failure and end stage renal disease (Safety Set – Subgroup 4)

		Age <18 years (N=33)		Age ≥ 18 years (N=132)		Total (N=165)	
		N	%	N	%	N	%
Patients with renal AEs	No	16	48.48	63	47.73	79	47.88
	Yes	17	51.52	69	52.27	86	52.12
Patients with acute renal failure	No	33	100	132	100	165	100
Patients with end stage renal disease	No	33	100	132	100	165	100

AEs=Adverse events
Only renal AEs reported in the retrospective period were considered.
Terms were codified with MedDRA dictionary, version 18.1.
Subgroup 4: Patients who reported renal AEs or confirmed notable renal laboratory values during the retrospective period.
Source: Table 14.3.1-6

Of the 87 patients experiencing a renal adverse event, 34 (39.08%) were in the ≥ 1000 ug/L and <2500 ug/L ferritin level group, 25 (28.74%) were in the ≥ 500 ug/L and <1000 ug/L group and 17 (19.54%) were in the ≥2500 ug/L group. Ten of the 87 patients (11.49%) were in the < 500 ug/L group and one (1.15%) did not have a ferritin value Ten of the 27 patients (37.04%) with SF < 500 ug/L, 25 of the 46 patients (54.35%) with SF ≥ 500 ug/L and <1000 ug/L, 34 of the 58 patients (58.62%) with SF ≥1000 ug/L and <2500 ug/L, and 17 of the 34 patients (50%) with SF ≥ 2500 ug/L had a renal adverse event.

In patients under 18 years of age, 1 of the 2 patients (50.00%) with SF < 500 ug/L, 5 of the 8 patients (62.50%) with SF ≥ 500 ug/L and <1000 ug/L, 8 of the 16 patients (50.00%) with SF ≥1000 ug/L and <2500 ug/L, and 4 of the 8 patients (50.00%) with SF ≥ 2500 ug/L had a renal adverse event.

CHMP comment : One of the 2nd objectives of this study is to evaluate the frequency of renal adverse events from the time of completion/discontinuation of the registration study to the end of the retrospective study.

The most common AEs were nephrolithiasis in both age groups (11.52% of patients aged 18 or older and 9.23% of patients under 18 years of age), renal colics, especially among patients aged 18 or older (11.52 % in group "≥ 18 years" and 4.62% in group "< 18 years"), followed by abnormal/increased urine protein/creatinine ratios, abnormal/increased blood creatinine, and proteinuria. Eight patients (2.84% of Safety Set) experienced serious renal AE including one child (patient 02_020).

Of note, among the serious renal AEs, there were 2 nephrolithiasis, 2 renal colics, and blood creatinine increased, acute kidney injury, haematuria (in a paediatric patient), hydronephrosis, renal failure and urethral stenosis (each one). Renal colics, one case of nephrolithiasis, one acute kidney injury in a context of pancreatitis and one haematuria occurred within a therapy included deferasirox. No new safety concern emerges from these data.

The MAH should clarify the definition of "distinct renal AEs by LLT" and clarify what is the difference with the total number of renal AEs.

No new safety concerns emerges from these descriptive data. However, the interpretation of these data is difficult as we do not known the percentage of patients taking deferasirox (monotherapy / sequential/concomitant) during the retrospective period.

Deaths

Sixteen patients died during the retrospective period (after completion/discontinuation of the registration trial). No information regarding date or cause of death was collected in the database. Renal parameters were collected for these patients but no information regarding date or cause of death was collected in the database.

CHMP comment

Age of deceased patients is between 20 and 86 years-old (at Q1). Main deaths occurred in patients enrolled in study 108/E (9/16 ; 56%). We regret that no information of the cause of death was collected in the database for this retrospective study. This cannot allow to conclude if any renal AE had a fatal outcome.

Serious Adverse Events (SAEs)

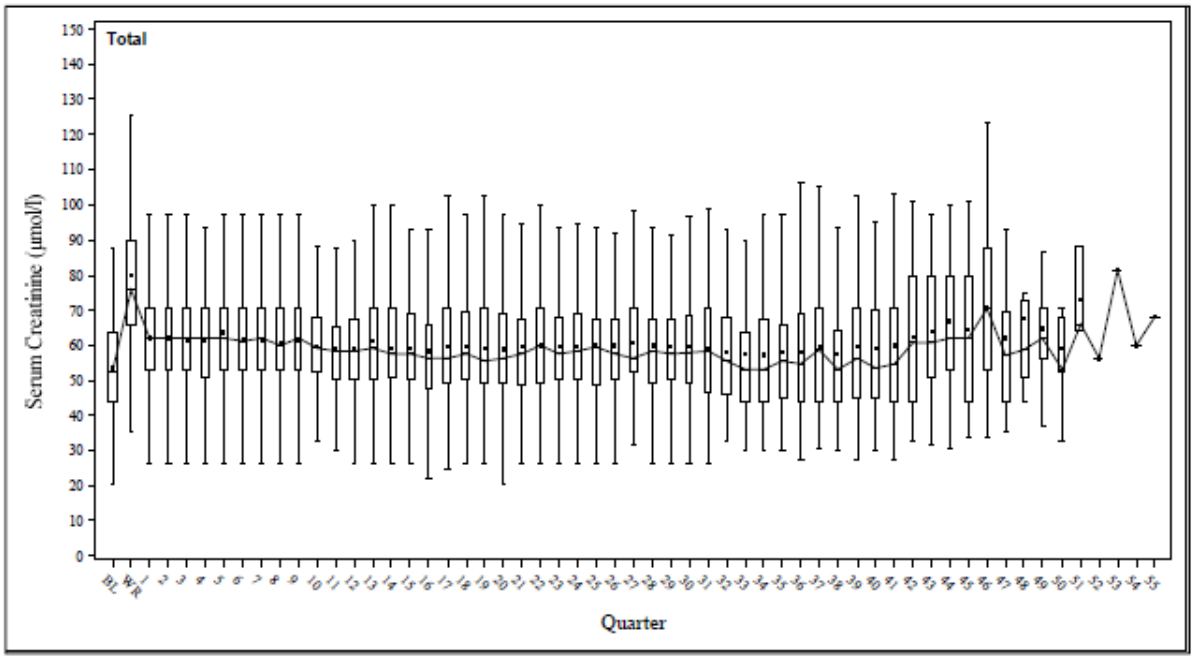
The collection of individual AEs/SAEs was not required for this type of retrospective study. Only renal adverse events and abnormal laboratory values or test results were collected.

Serum creatinine

In the Safety Set, the SCr mean baseline value for the registration studies was 53.39 ± 13.45 µmol/l (range: 20.35 – 87.96 µmol/l) while the worst value was on average 79.73 ± 20.19 µmol/l (range: 35.40 – 156.50 µmol/l). During the retrospective period, mean/median values were slightly higher than baseline values but lower than worst values. SCr values remained quite stable (around 60 µmol/l in mean) until Quarter 43, when the number of observed patients began to drop considerably (37 or less) and mean/median values started to fluctuate.

Mean/median values for patients aged ≥18 years were slightly higher than those reported for patients aged less than 18 years

Figure 5-5 Serum creatinine by visit (Safety Set)



Source: [Study ICL670AIT14-Figure 14-3-2.1]

In the pediatric group, mean baseline and worst values were equal to 41.30 ± 9.73 µmol/l (range 20.35 – 69.84 µmol/l) and 65.73 ± 13.23 µmol/l (range 41.50 – 107.80 µmol/l) respectively. Mean/median values during the retrospective period were stable (mostly between 50 and 60 µmol/l in mean) and slightly lower than the ones reported for adults. Since SCr was recorded as absolute value, the slightly higher values in the adult population reflect the normal absolute increase in SCr related to growth and muscle mass.

CHMP comment

The primary objective of this study was to evaluate the trend of serum creatinine over time in patients who were treated with at least one dose of deferasirox during registration studies. There was no primary efficacy analysis for this study.

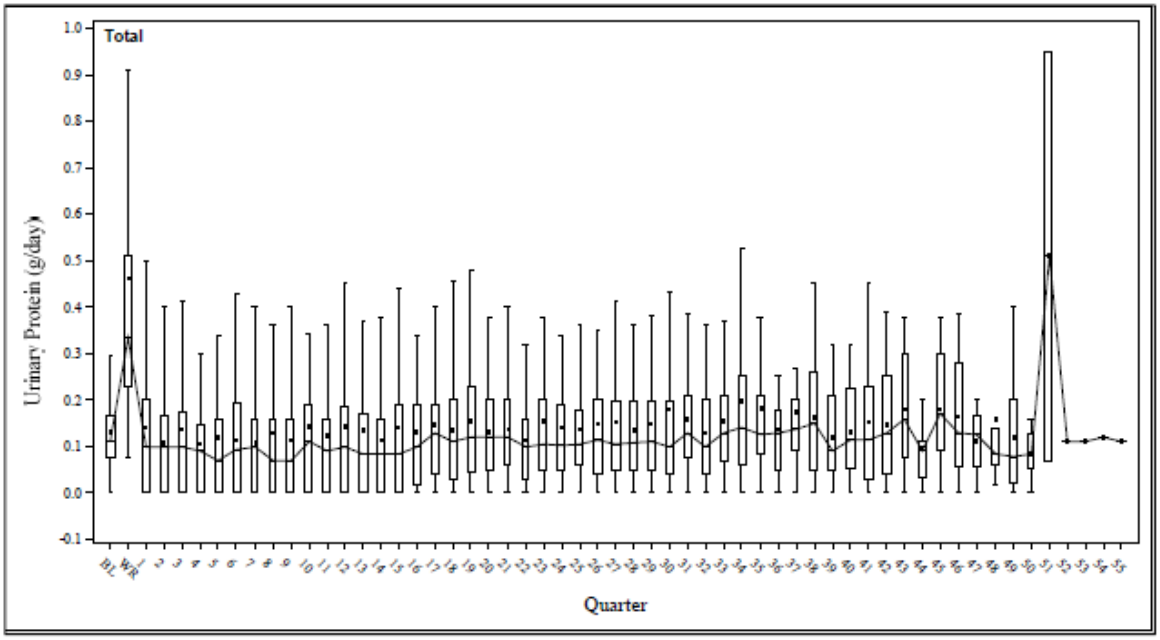
During the retrospective period, mean/median SCr values were slightly higher than baseline values but lower than worst values and relatively stable (around 60 µmol/l in mean) until Quarter 43, when the number of observed patients began to decrease notably. No significative difference was observed between paediatric and adults group.

No firm conclusions on the long term safety of deferasirox could be drawn from these descriptive data as the safety set contains only 5 patients treated with deferasirox. The other patients could receive either deferasirox with other chelators (sequential/ concomitant) or monotherapies of other chelators.

Urinary Protein

Mean baseline and worst values for urinary protein during the registration studies were equal to 0.13 ± 0.08 g/day (range 0.00 – 0.60 g/day) and 0.46 ± 0.72 g/day (range 0.08 – 11.26 g/day) respectively, with mean baseline value considered within normal range. Less than 25% of data in the retrospective period were available, but mean/median values were in any case mostly higher than values at baseline but lower than worst values for the registration studies and within normal range. The marked spike in the graph at Q51 reflects the results in only two patients. (Figure 5-8)

Figure 5-8 Urinary protein by visit (Safety Set)



Source: [Study ICL670AIT14-Figure 14-3-2.2]

The separate analyses of the two age groups (<18 years and ≥18 years) were inconclusive due to the small size of the groups.

Mean baseline and worst values for urinary protein during the registration studies were equal to 0.13 ± 0.08 g/day (range 0.04 – 0.49 g/day) and 0.44 ± 0.33 g/day (range 0.13 – 1.74 g/day). Quarterly values were consistently below mean worst value and mostly ≤ 0.15 g/day, occasionally reaching values between 0.16 and 0.19 g/day.

CHMP comment
Based on the figure 5-8, Urine protein values seems to be relatively stable. However, these results should be taken with caution as only based on 25% of values available in the retrospective period.

Urinary creatinine

Mean baseline value (of the registration trials) for the safety set was equal to 8.40 ± 3.70 mmol/day with a range between 1.90 and 25.50 mmol/day, and mean worst value (i.e. the highest urinary creatinine collected during the registration studies) equal to 16.83 ± 5.79 mmol/day (min. 6.70

mmol/day and max. 38.00 mmol/day). During the retrospective period, less than 15% of the data were collected, even at Quarter 1 (41 out of 282 patients had non - missing data), and no graphs were therefore produced. Values were around 9-10 mmol/day, higher than mean baseline value and lower than mean worst value.

In the pediatric population, mean baseline and worst value of the registration studies were equal to 7.11 ± 3.08 mmol/day (range 1.90 – 16.40 mmol/day) and 13.96 ± 5.11 mmol/day (range 7.10 – 29.30 mmol/day) respectively. Quarterly values in the retrospective period were mostly between 7 and 10 mmol/day.

CHMP comment
Urinary creatinine values during the retrospective period are between the baseline and worst values observed in registration studies. However, these results are based on only 15% of values available in the retrospective period and should be taken with caution.

Urinary protein/creatinine ratio

The mean baseline and worst urinary protein/creatinine ratios for the safety set were equal to 0.15 ± 0.12 (range 0.00 – 1.53) and 0.53 ± 1.47 (range 0.10 – 24.48) respectively. As for urinary protein and urinary creatinine, few data were available during the retrospective period (more than 85% of the data were missing). The highest mean values were 0.47 ± 1.44 (range 0.00 -7.67) at Quarter 5 (mean calculated on 42 patients) and 0.96 ± 1.55 (range 0.08 – 4.38) at Q46 (mean calculated on 7 patients) (Figure 5-10).

In patients under 18 years of age, mean baseline value and worst value in the registration studies were equal to 0.17 ± 0.07 (range 0.05 – 0.36) and 0.53 ± 0.41 (range 0.13 – 2.17) respectively. Quarterly values for mean/median urinary protein/creatine during the retrospective period were mostly near baseline value of the registration study.

CHMP comment
Similarly, no conclusion can be drawn from these UPCR results as more than 85% of the UPCR values are missing.

Creatinine clearance

In clinical practice, Creatinine Clearance (CrCl) is estimated based on SCr using the Cockcroft-Gault or Schwartz Equation for monitoring renal function. The study protocol mandated documentation of SCr but did not mandate to document serum creatinine clearance. CrCl was collected only if available, in addition to SCr and UPCR, to provide further indications about renal function during the retrospective period of this chart review. The weight of patients was not available in the same time of SCr value to calculate the clearance. When analyzing the data however, only few creatinine clearance values were available in the database, and therefore no reliable considerations could be drawn.

CHMP comment
We regret that Creatinine clearance values were not available as it is a good parameter to assess renal function.

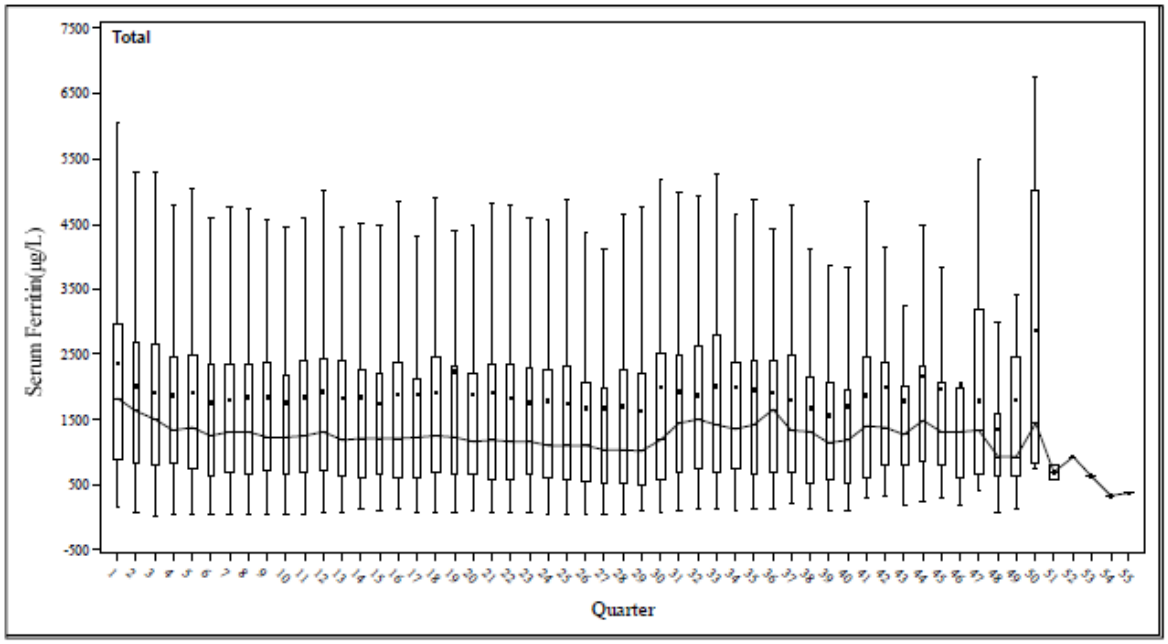
Hemoglobin

Mean hemoglobin values during the retrospective period were very low and persistently lower than 100 g/l considering the quarters with a meaningful number of data collected.

Serum ferritin

Median serum ferritin at Q1 was 1,829.00 µg/l (range 155.00 – 14,258.00 µg/l) in the safety set and 2,055.00 µg/l (range 360.00 – 7,446.00 µg/l) in patients under 18 years of age. Levels tended to drop initially and then fluctuate slightly from quarter to quarter.

Figure 5-12 Serum Ferritin (Safety Set)



Source: [Study ICL670AIT14-Figure 14-3-2.15]

CHMP comment
Serum ferritin values varies similarly in both total population and paediatric population. However, the impact of ferritin on serum creatinine variations cannot be established based on these descriptive data.

Long-term use

This study assessed the renal function of patients enrolled in the registration studies up to 13 years later and confirmed the non-progressive nature of these serum creatinine observations. The primary objective of the study was to evaluate the trend of serum creatinine over time in patients previously treated with at least one dose of deferasirox during the previous registration studies and found that the serum creatinine was stable throughout the retrospective study. The efficacy and safety data from this study are consistent with the long -term pivotal studies up to 5 years.

According to the MAH, recently submitted data from two long-term observational studies with 3-year follow-up in pediatric and adult patients, and 5-year follow-up in pediatric patients (studies CICL670A2301 and A2411 respectively) confirm these conclusions; no unexpected safety findings were observed regarding AEs or laboratory abnormalities, and the overall safety profile of deferasirox was consistent with the approved label. Notable increases in SCr were observed in some patients and the overall SCr increase was consistent with that of a growing pediatric patient. No over-proportioned progressive increase in SCr was observed.

In the 5-year registry with deferasirox DT (CICL670A2411) in children aged 2 to less than 6 years, the overall safety profile of deferasirox was consistent with that described in the approved SmPC at enrollment, and it suggests that deferasirox does not impact overall growth or sexual development in observed in pediatric patients.

The findings observed from this study were consistent with the five-year renal data from the pivotal registration study, Study CICL670A0107, indicating no progressive worsening of the renal function over time.

CHMP comment

Overall, no unexpected safety findings have been identified in the study 2301, in comparison to the overall safety profile of Exjade® described in the approved label. For serum creatinine, creatinine clearance and ALT, which are specific endpoints of the primary objective of this study, the MAH provide boxplot by quarter for all patients enrolled in the Safety Set which permit to have an idea of the trend of these values over the three years of treatment with deferasirox. Globally, the evolutions of these biological markers are reassuring. Similarly, based on the results of the study A2411, there were no unexpected safety findings observed regarding the long term use of Exjade®.

The retrospective study AIT14 is the 1st study with a large follow-up of patients enrolled in registration studies (up to 13 years later). More than 90% of both the total population and pediatric population were observed for at least seven years following the completion of/discontinuation from the previous registration trials. This study did not reveal any new safety concern regarding renal parameters (in adults/paediatric patients). However, these results should be taken with caution due to the nature "retrospective" and "descriptive" of the study.

Safety conclusion

A total of 282 patients were included in the Safety Set including 23.05% of paediatric patients at Q1 of data collection. The duration of treatment with deferasirox was 3.45 ± 1.59 years (range: 0.02 – 6.36 years) in the registration studies and 6.11 ± 2.84 years (range: 0.002 – 13.36 years) in the retrospective period. More than 50% of the patients were treated with deferasirox for at least 7 years during the retrospective period. Overall, the treatment duration was 7.88±4.25 years (range: 0.03 – 14.14 years); more than 50% of the patients were treated with deferasirox for at least 9 years.

The mean baseline and worst urinary creatinine values during registration were 8.40 ± 3.70 mmol/day and 16.83 ± 5.79 mmol/day respectively, and between 9.00 and 10.00 mmol/day during retrospective collection.

Renal AEs were reported in 30.50% patients of the overall safety set, in 26.15% of the patients under 18 years of age and in 31.80% of those 18 or older. Eight patients (2.84%) had at least one serious renal AE (seven patients aged ≥ 18 years and one patient aged less than 18), none of which were suspected of being related to treatment with deferasirox. Seven (2.48%) patients had a renal AE of severe intensity (Six patients aged ≥ 18 years and one patient aged less than 18) and five (1.77%) discontinued treatment with deferasirox due to renal AEs (all aged 18 years or older).

Almost 60% of the patients experiencing a renal AE during the retrospective period took one concomitant medication with nephrotoxic effect within 6 months prior to the occurrence of the first event between renal adverse event and notable renal laboratory value.

Thirty-three patients (11.70%) had at least one AE suspected of being related to deferasirox.

None of the deferasirox-related AEs were serious, all but three were mild to moderate in intensity, and in most cases deferasirox was temporarily interrupted or dosage was adjusted and no further action was required.

2.3.3. Discussion on clinical aspects

This study is a retrospective chart review of patients with transfusional hemosiderosis enrolled in the deferasirox registration studies (CICL670A0105,106,107,108 and 109) and were treated with at least one dose of DFX. The primary objective of this study was to evaluate the trend of serum creatinine over time in those patients. The long term renal safety is also one of this study's objectives.

According to the MAH, SCr was stable throughout the retrospective study until Q42, the last quarter with a meaningful amount of available data, and mean values of SCr were around 60 µmol/l, slightly higher than the mean baseline value but lower than the mean worst value of the registration studies. These results, in patients exposed to deferasirox an average of roughly 10 years, further substantiates the reversibility and non-progressive nature of treatment effect on renal function. Within the limits of this study related to the lack of data, other renal parameters (urinary protein, urinary creatinine, urinary protein/creatinine ratio) also appeared to be stable throughout the retrospective period, with values below the worst value reported in the registration studies. It seems, based on the data provided, that no significative difference was observed between paediatric and adults groups.

Finally, only eight patients (2.84%) had at least one serious renal AE, none of which was suspected of being related to treatment with deferasirox. Thirty-three patients (11.70%) had AEs suspected of being related to deferasirox, which in most cases were mild to moderate in intensity and were managed without the need to discontinue treatment permanently. The deferasirox clinical trial program reported increases in SCr and renal adverse events in patients treated with deferasirox, concluding however that the changes in SCr were dose - dependent and non-progressive with up to 5 years of follow-up, and that renal events were manageable with monitoring and dose adjustments and were reversible upon discontinuation.

We acknowledge that this retrospective chart review was a unique opportunity to collect historical data from patients enrolled in registration studies, especially as more than 90% of the population were observed for at least 7 years after completion of registration studies. However, interpretation of these data is difficult due to limitations such as the nature "retrospective" and "descriptive" of the study, the lack of data available for key renal parameters such as UPCR and CrCl, the methodology used for treatment duration calculation. Also, data from safety set cannot allow to assess the role of deferasirox on the variation of renal parameters over time as patients received either multiple iron chelators (sequential/concomitantly) or other iron chelators (deferoxamine, deferiprone,..).

Also the main secondary objectives to evaluate renal function parameters in patients who had been treated with only deferasirox could not be reached due to the lack of patients in this subgroup (n=5). Therefore no conclusion could be drawn on the long term safety of deferasirox based on the results of this study.

3. Rapporteur's overall conclusion and recommendation

This study is a retrospective chart review of patients with transfusional hemosiderosis enrolled in the deferasirox registration studies (CICL670A0105,106,107,108 and 109) and were treated with at least one dose of DFX. The primary objective of this study was to evaluate the trend of serum creatinine over time in those patients. The long term renal safety is also one of this study's objectives.

We acknowledge that this retrospective chart review was a unique opportunity to collect historical data from patients enrolled in registration studies, especially as more than 90% of the population were observed for at least 7 years after completion of registration studies. However, interpretation of these data is difficult due to some limitations such as the nature "retrospective" and "descriptive" of the study, the lack of data available for key renal parameters such as UPCR and CrCl, the methodology used for treatment duration calculation. Also, data from safety set cannot allow to assess the role of deferasirox on the variation of renal parameters over time as patients received either multiple iron chelators (sequential/concomitantly) or other iron chelators (deferoxamine, deferiprone,..).

Also the main secondary objectives to evaluate renal function parameters in patients who had been treated with only deferasirox could not be reached due to the lack of patients in this subgroup (n=5). Therefore no conclusion could be drawn on the long term safety of deferasirox based on the results of this study.

☒ **Not fulfilled:**

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

4. Additional clarification requested

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

1- The MAH should provide a clear justification of the methodology used for the treatment duration calculation with the reason why temporary interruptions in treatment during the registration and retrospective periods were not excluded from the calculation and should

provide an accurate estimation of the treatment duration with deferasirox (in patient-year) for the safety set (respectively for adults and paediatric patients).

2- The MAH should justify for having chosen mean change vs worst value instead of baseline value. This should be done and detailed interpretation should be provided.

3- Instead of having the mean change in absolute value vs worst value, it would have been more appropriate to have the percentage of SCr changes compared to baseline at registration enrollment for each quarter. The MAH should provide such data for SCr changes (as well as CrCl changes) for each quarter for safety subgroups 2, 3 and 4. A subanalysis for respectively for adults and paediatric patients should be also provided.

4- Of the 197 patients in safety subgroup 3, we do not known the percentage of patients taking deferasirox (monotherapy / sequential/concomitant) during the retrospective period. The MAH should clarify and discuss if any renal deterioration is observed in each subgroup taking deferasirox (monotherapy / sequential / concomitant) compared with baseline. A subanalysis for respectively for adults and paediatric patients should be also provided.

5- In the safety subgroup 4, a total of 87 patients (52.41% of subgroup 4) were affected by renal AEs in the retrospective period including 18 paediatric patients (<18 years-old). No details were provided on the nature of renal AEs in this subgroup. In addition a discrepancy was noted with table 14.3.1-6 where a total of 86 patients experienced renal AE (52.12%). The MAH should clarify.

6- It would be appreciated that the MAH performed a comprehensive safety analysis in the safety subgroup n°4 with a description of renal AEs and notable renal function parameters by type of patients (i.e patients on deferasirox only, on multiple chelators (by different combinations), other single chelators (deferoxamine, deferiprone). A subanalysis for respectively for adults and paediatric patients should be also provided.

7- The MAH should clarify the definition of "distinct renal AEs by LLT" and clarify what is the difference with the total number of renal AEs.

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

5. MAH responses to Request for supplementary information

1- The MAH should provide a clear justification of the methodology used for the treatment duration calculation with the reason why temporary interruptions in treatment during the registration and retrospective periods were not excluded from the calculation and should provide an accurate estimation of the treatment duration with deferasirox (in patient-year) for the safety set (respectively for adults and paediatric patients).

MAH's response

As a retrospective analysis of patients first exposed to deferasirox in the registration trials and their open-label extensions, this study was designed to measure the long-term renal safety in patients on deferasirox therapy regardless of exposure time and in real treatment practice.

In real treatment practice, patients are typically on iron chelation as a life-long, chronic therapy, where treatment interruptions are common and patients may be on and off treatment. Therefore, the true, long-term implications of deferasirox treatment on renal safety would not be reflective how patients are actually being treated in practice if the treatment interruptions were excluded from the calculation for treatment duration.

Additionally, as a non-interventional chart review, a specific ongoing treatment was not required; patients may have been treated with iron chelators or any other medication at the physician's discretion and according to local prescribing information. During the retrospective period patients have been exposed to iron chelators other than deferasirox, on and off, either as single agent or in combination treatment. As no single contribution to renal safety can be assessed, this time is also included in treatment duration.

Temporary interruptions are not normally excluded when calculating treatment duration. It should be noted that in all of the registration studies and their extensions (CICL670A105, 106, 107, 108, and 109), temporary interruptions were included as exposure. The calculations for treatment duration in Study AIT14 have remained consistent with the previously used statistical methodology during the core and extension phase of the respective registration studies. Further, temporary interruptions would not significantly impact the overall long-term treatment duration of up to 13 years, particularly in the context of assessing the long term renal safety of deferasirox with any exposure. Therefore, an analysis including interruption of deferasirox would not derive a new conclusion.

CHMP comment

The MAH has clarified that iron chelation is a long term therapy with patients under different types of iron chelators. Some of them may be on or off treatment in real life, depending of the disease evolution. The MAH cannot provide accurate estimation of the treatment duration with deferasirox in the patients enrolled in this study.

Therefore, the MAH has provided some clarifications but no accurate estimation of treatment duration with deferasirox could be obtained for the safety set limiting the interpretation of long term data.

2- The MAH should justify for having chosen mean change vs worst value instead of baseline value. This should be done and detailed interpretation should be provided.

MAH's response

The primary objective of this study was to observe the long-term trends of serum creatinine (SCr) in patients exposed to at least one dose of deferasirox during the registration studies. Presenting the quarterly changes from the worst value reported during these studies is considered as appropriate in an effort to further substantiate the reversibility and non progressive nature of treatment effect on renal function.

See also response to question 3 for requested analysis and interpretation of renal parameters.

CHMP comment
The MAH has clarified the fact to have chosen mean change vs worst value is due to further substantiate the reversibility and non progressive nature of treatment effect on renal function. In our point of view, mean changes vs baseline value could be also useful to follow these renal parameters' evolution.

3- Instead of having the mean change in absolute value vs worst value, it would have been more appropriate to have the percentage of SCr changes compared to baseline at registration enrollment for each quarter. The MAH should provide such data for SCr changes (as well as CrCl changes) for each quarter for safety subgroups 2, 3 and 4. A subanalysis for respectively for adults and paediatric patients should be also provided.

MAH's response

Analyses have been carried out to present the quarterly changes of SCr from baseline of the registration studies instead of from worst values. The results for safety groups 2, 3 and 4 are presented separately for adult and pediatric patients. As mentioned in the clinical study report, only few creatinine clearance values were available and no reliable considerations could be drawn from them. Therefore, the CrCl by quarterly changes from baseline cannot be provided as requested. Available CrCl were provided in table 14.3.2.5 of the study AIT14 CSR.

<u>Study subgroup 2:</u> Patients (N=62) who were on multiple chelators (concomitantly or at different times) and other single chelators (deferoxamine, deferiprone, etc.) except deferasirox during the retrospective period

The mean changes from baseline in serum creatinine (SCr) collected quarterly in the retrospective period for the overall, adult and pediatric populations are collected and shown in Figure 2-1.

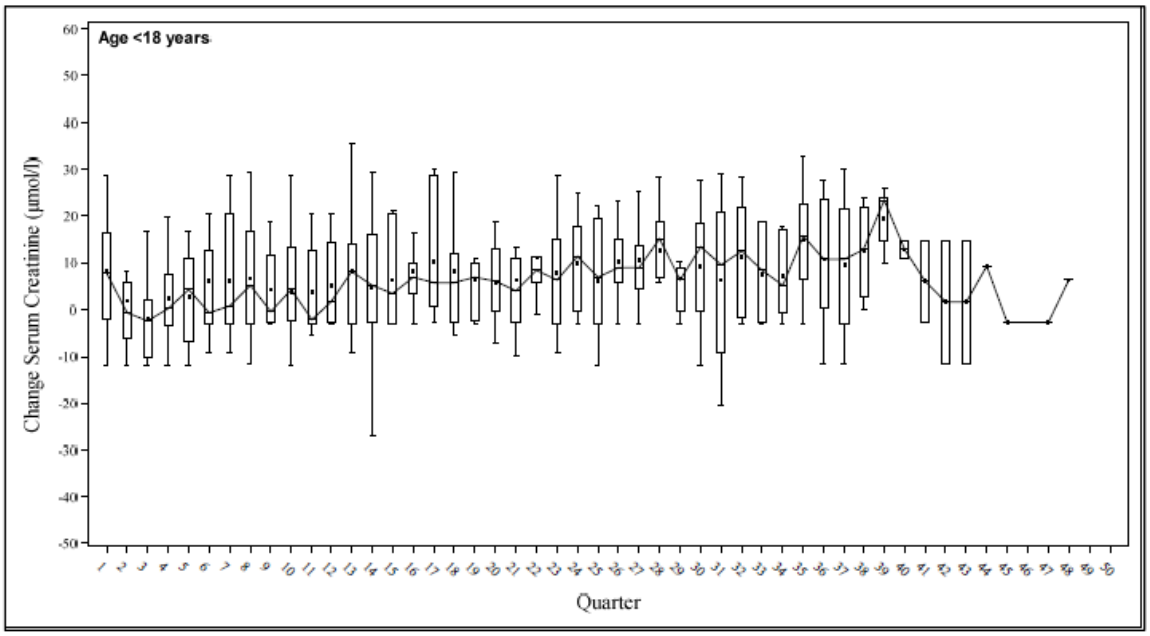
The mean baseline SCr value was 56.44 ± 10.62 µmol/l overall (range 33.15 – 78.08 µmol/l), 58.69 ± 9.98 µmol/l (34.45 – 78.08 µmol/l) for patients 18 years or older, and 47.06 ± 7.96 µmol/l (33.15 – 62.32 µmol/l) for patients under 18 years of age. Given that 50 of the 62 patients in this subgroup were adults, the results of this age class closely reflect those of the overall subgroup.

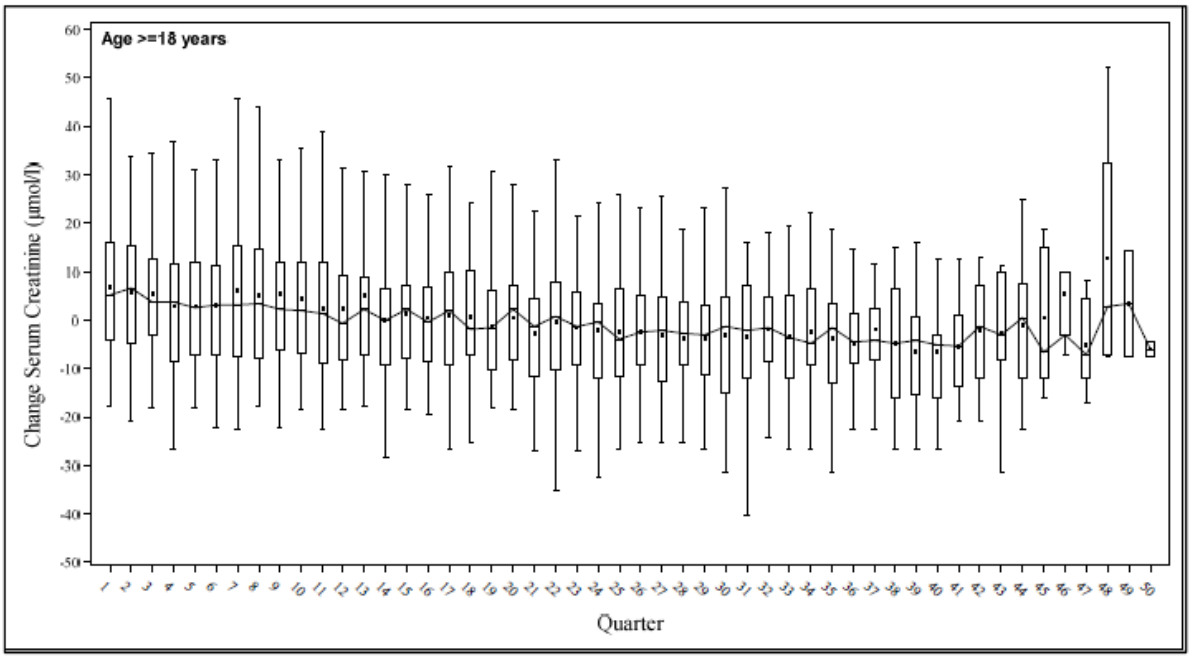
During the retrospective period, the trend in mean SCr values in the adult population was essentially **stable** until Quarter 45, after which only six patients at most were still under observation and mean/median values fluctuated considerably.

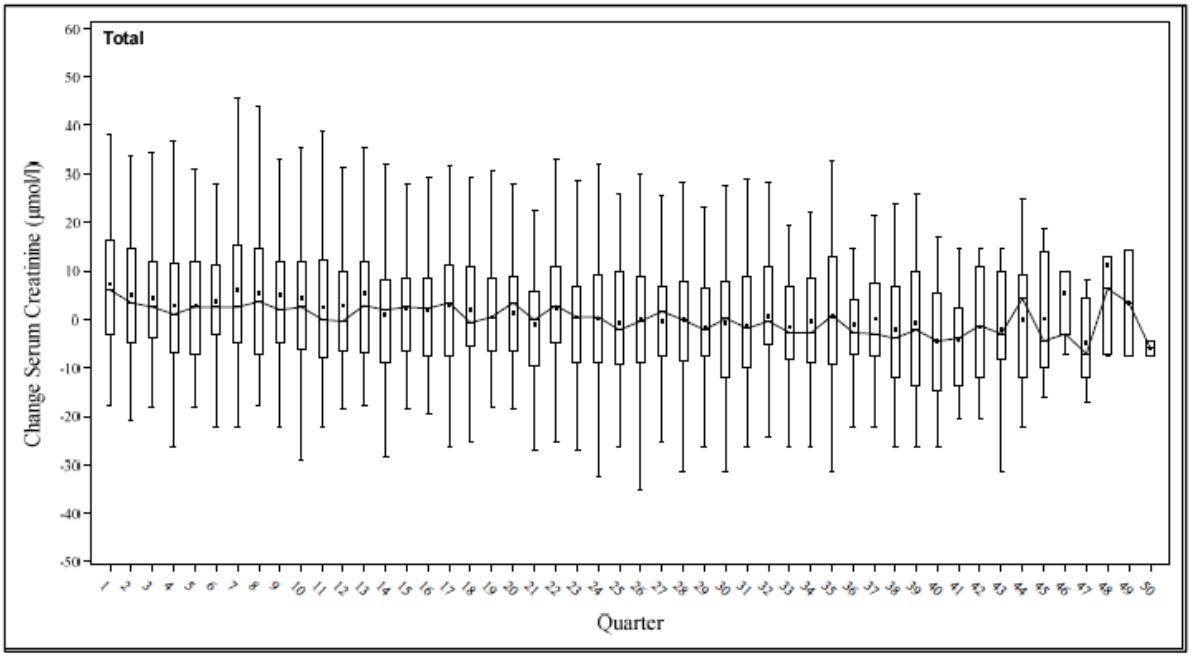
Mean SCr values were slightly higher than baseline (60-65 µmol/l) from Q1 to Q20, with mean changes from baseline of around 2-5 µmol/l. Percent changes from baseline ranged from 6% to 13% from Q1 to Q13 and from 2% to 3% from Q14 to Q20, except for a small negative change from baseline (-1.26 µmol/l – -0.99%) at Q19. SCr values were then slightly lower than baseline (53 -60 µmol/l) from Q21 to Q45, with negative mean changes mostly between 0 and -4 µmol/l (0% to -10%). Twelve (12) patients made up the pediatric population in this subgroup (patients less than 18 years old at Q1). Until Q12, mean creatinine values were mostly between 50 -55 µmol/l, with an increase from baseline of around 2-5 µmol/l (7-17%), except at Q3, during which SCr values presented a mean negative change from baseline (-2.18 µmol/l – -3.12%). From Q13 on, mean values were slightly higher (54 and 60 µmol/l) with percent changes from baseline mostly between 14% and 30%. According to the MAH, these higher values may, however, reflect the normal proportional increase in SCr absolute values related to the greater body muscle mass as pediatric subjects grew over the observation period.

According to the MAH, these trends suggest that the administration of at least one dose of deferasirox during the registration studies, followed by a single chelator other than deferasirox (deferoxamine, deferiprone, etc.) or by combinations of iron chelators other than deferasirox (concomitantly or at different times) during the retrospective period, did not have a general long -term effect on renal function.

Figure 2-1 **Serum creatinine: change vs. baseline value in the registration studies (Safety Set – Subgroup 2)**







The markers inside the boxes indicate the mean values and the lines connect the median values. The length of the boxes represent the distance between Q1 (25th percentile) and Q3 (75th percentile); the whiskers represent the minimum values above 1.5 × IQR below Q1 and maximum values below 1.5 × IQR above Q3.

IQR is the interquartile range, i.e. the distance between Q1 and Q3.

Safety Set - Subgroup 2: Patients who were on multiple chelators and other single chelators except deferasirox during the retrospective period.

Source: Appendix 1- ICL670AIT14-Tables and Figures document

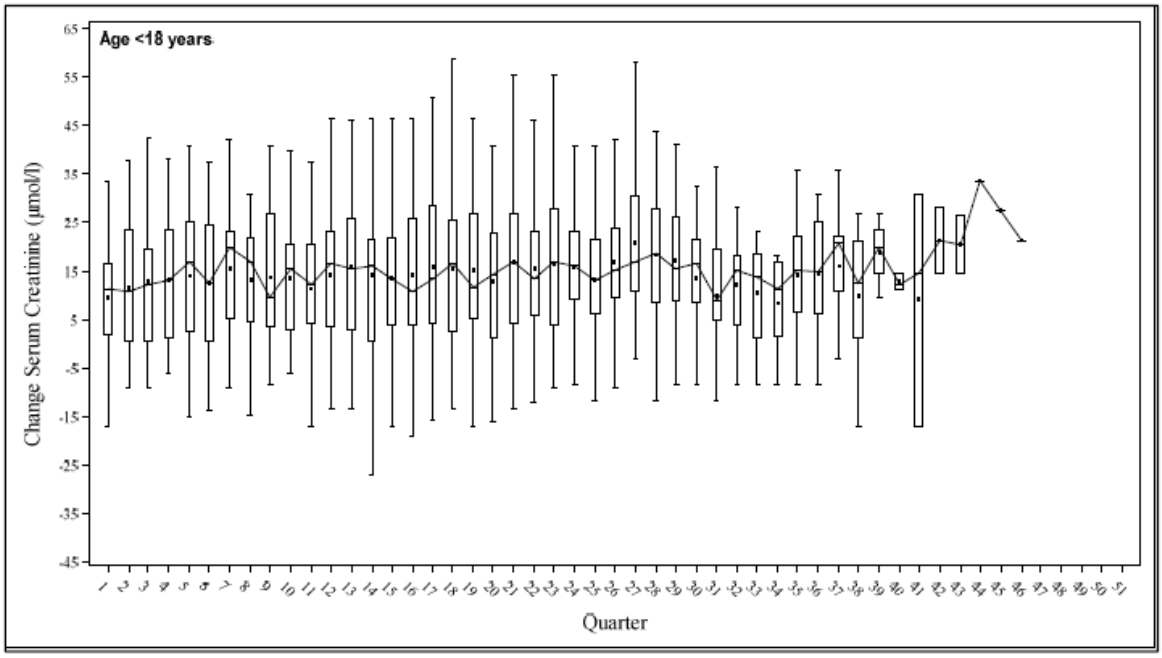
Study subgroup 3: Patients (N=197) who reported renal Adverse Events (AE) or confirmed notable renal laboratory values during the registration studies.

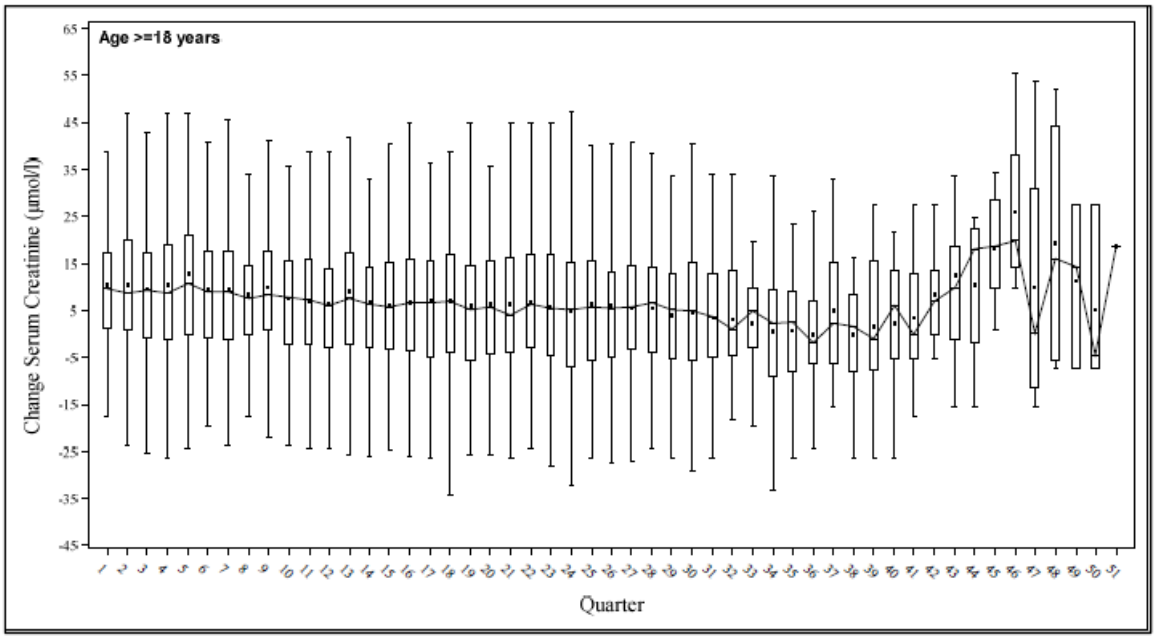
The mean changes from baseline in serum creatinine collected quarterly in the registration period for the overall, adult and pediatric populations are collected and shown in Figure 2-2.

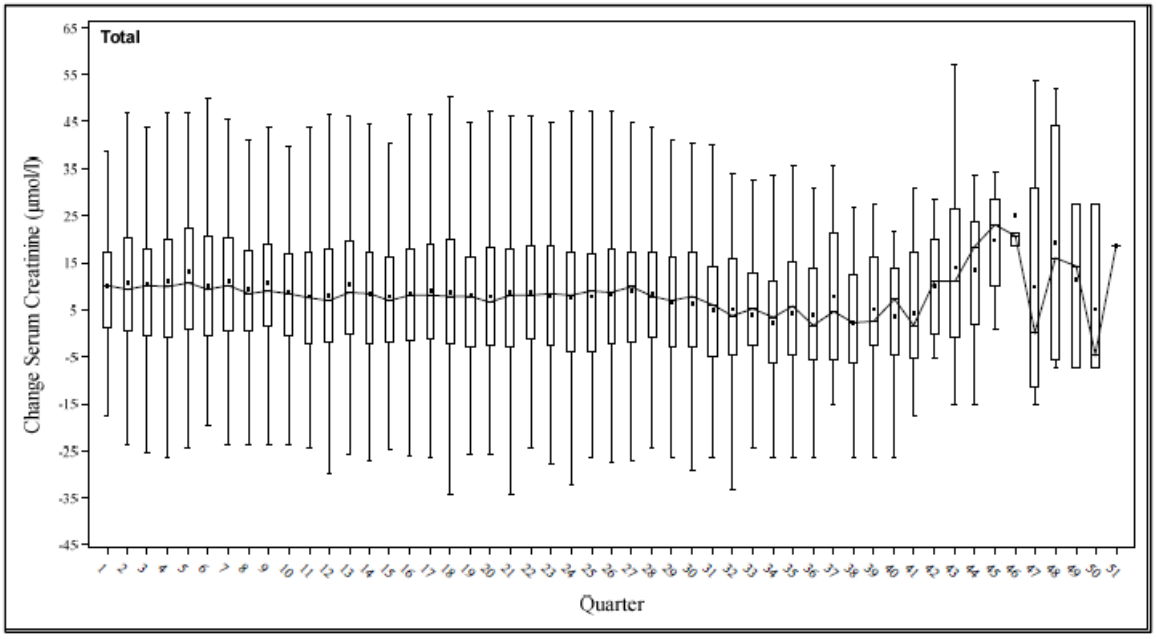
Mean SCr at baseline of the registration studies was 53.23 ± 13.72 µmol/l overall (range 26.10 – 87.96 µmol/l), 56.90 ± 12.74 µmol/l (range 30.95 – 87.96 µmol/l) in adults (N=154), and 40.10 ± 7.84 µmol/l (range 26.10 – 62.32 µmol/l) in pediatric patients (N=43). Until Q28 of the retrospective period, mean SCr values in the adult population were consistently between 62-67 µmol/l, with **mean change from baseline between 5 and 10 µmol/l, corresponding to a percent change of 12-21%** (except for a spike at Q5: mean value 69.44 µmol/l and change from baseline 12.83 µmol/l – 27.15%). From Q29 to Q41, mean values then fell progressively, reaching values close to or equal to baseline (change from baseline 0-4 µmol/l – 0-9%) before starting to vary considerably due to the small number of subjects still under observation.

The trend for the <18 age class of this subgroup was also quite constant, with mean SCr values between 50 and 56 µmol/l and a change from baseline of 10-16 µmol/l (27-42%), although Quarters 26-29 presented slightly greater changes (17-20 µmol/l – 44-54%). These trends indicate that renal adverse events occurring during the registration studies overall did not provoke irreversible or progressive long-term effects on renal function.

Figure 2-2 **Serum creatinine: change vs. baseline value in the registration studies (Safety Set – Subgroup 3)**







The markers inside the boxes indicate the mean values and the lines connect the median values. The length of the boxes represent the distance between Q1 (25th percentile) and Q3 (75th percentile); the whiskers represent the minimum values above 1.5 × IQR below Q1 and maximum values below 1.5 × IQR above Q3.

IQR is the interquartile range, i.e. the distance between Q1 and Q3.

Safety Set - Subgroup 3: Patients who reported renal AEs or confirmed notable renal laboratory values in registration studies.

Source: Appendix 1- ICL670AIT14-Tables and Figures document

Study subgroup 4: Patients (N=165) who reported renal AEs or confirmed notable renal laboratory values during the retrospective period

The mean changes from baseline in serum creatinine collected quarterly in the retrospective period for the overall, adult (N=132) and pediatric (N=33) populations are collected in Table 14.3-2.21 of the Appendix 1- ICL670AIT14-Tables and Figures document and are shown in Figure 2-3.

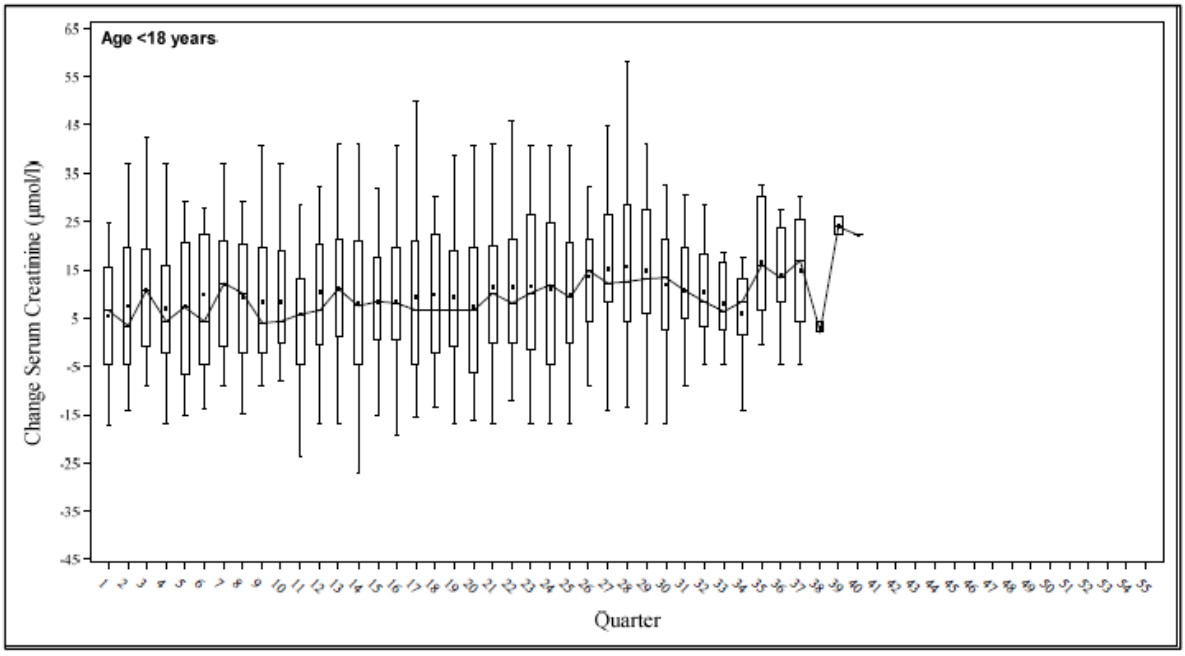
Mean SCr at baseline of the registration studies was 54.85 ± 13.31 overall (range 28.30 – 87.96 µmol/l), 58.01 ± 12.37 µmol/l (range 30.95 – 87.96 µmol/l) in adults, and 42.21 ± 8.70 µmol/l (range 28.30 – 67.18 µmol/l) in patients <18 years.

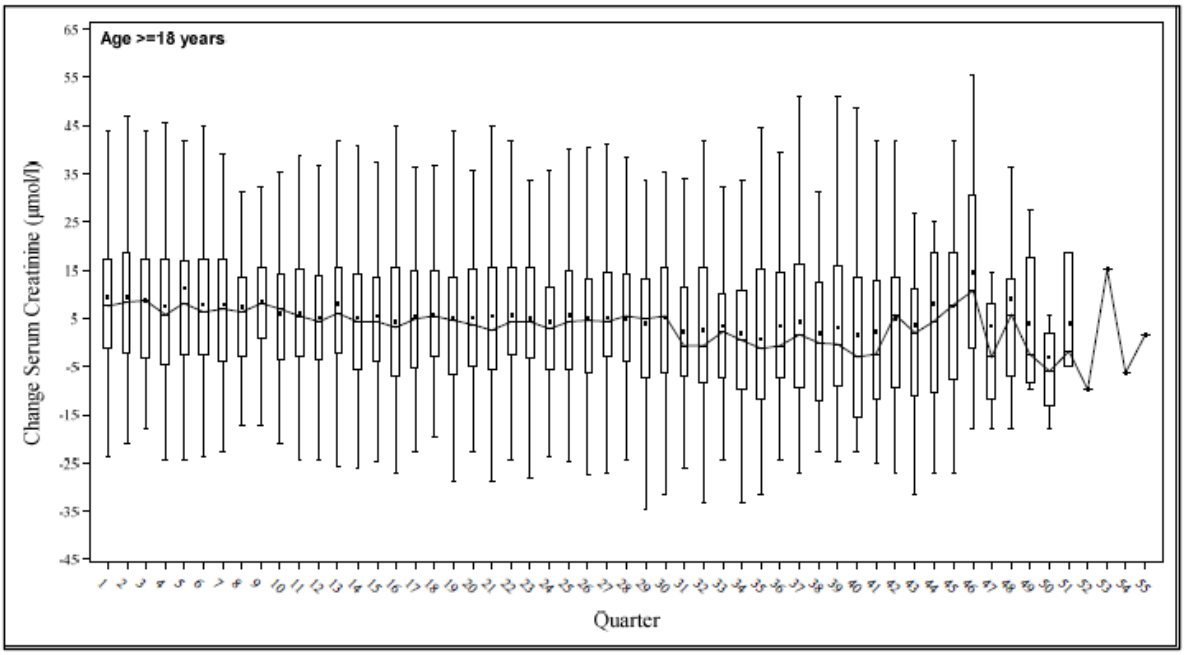
As in subgroup 2 and subgroup 3, there were no marked changes in the SCr values of adults over the retrospective period, at least until the last quarters of data collection c haracterized by few available data. Mean SCr values were around 65-67 µmol/l with a change from baseline of 7-9 µmol/l (11-18%) until Q13, with a small spike of 69.22 µmol/l (change from baseline 11.30 µmol/l – 23.6%) at Q5. Values were then slightly lower and consistently between 62 and 63 µmol/l, with a change from baseline of 4-5 µmol/l (9-13%) between Q14 and Q30, and even lower between Q31 and Q36 (60-62 µmol/l – change from baseline 1-3 µmol/l = 3-8%), before rising slightly in the subsequent quarters.

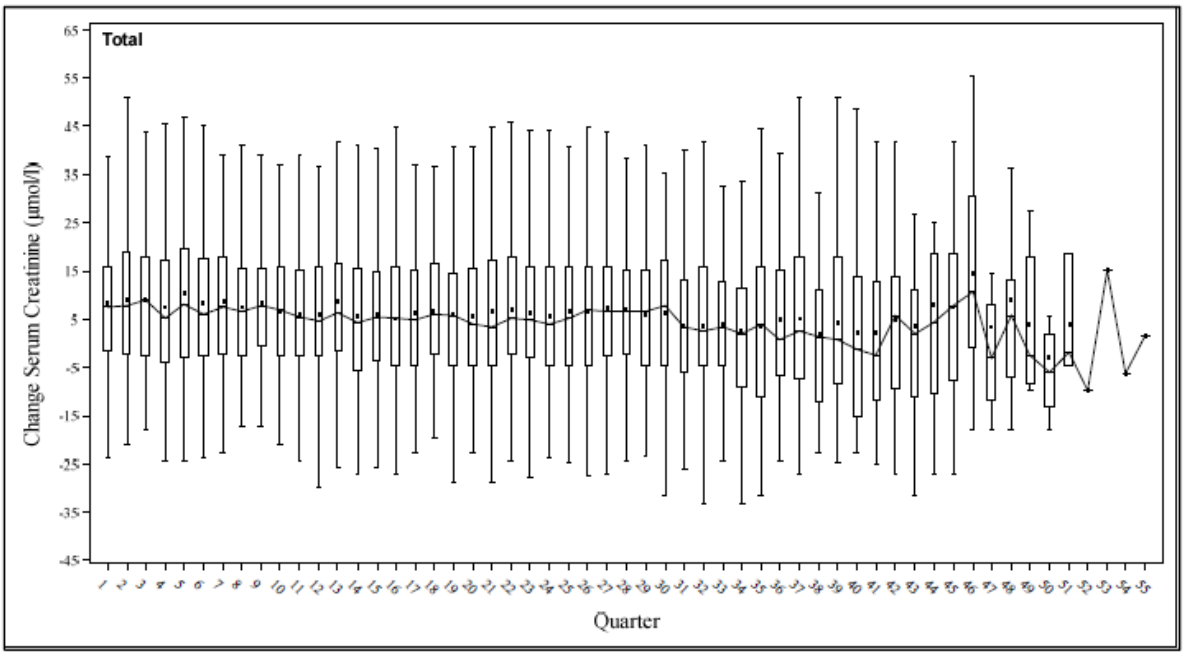
Mean values in the pediatric population were stable and around 49-51 µmol/l, with changes from baseline of 8-9 µmol/l (17-29%) until Q20. Small spikes are visible in the graph at Q7, Q12 and Q13 and correspond to values of 52-53 µmol/l with change from baseline of 10-11 µmol/l (29-33%). These latter values were again observed between Q21 and Q25. Mean changes after Q25 tended to be higher (13-16 µmol/l – 36-40%) until Q29, only to return to values between 6 and 16 µmol/l between Q30 and Q37. The overall slight trend to higher absolute SCr values over years in time is in line with the physical development of a growing pediatric population.

SCr changes versus baseline were comparable between total subgroup 4 with renal AEs, occurring during the retrospective period, and total subgroup 3 and 2, with all of them showing overall stability.

Figure 2-3 Serum creatinine: change vs. baseline value in the registration studies (Safety Set – Subgroup 4)







The markers inside the boxes indicate the mean values and the lines connect the median values. The length of the boxes represent the distance between Q1 (25th percentile) and Q3 (75th percentile); the whiskers represent the minimum values above 1.5 × IQR below Q1 and maximum values below 1.5 × IQR above Q3.

IQR is the interquartile range, i.e. the distance between Q1 and Q3.

Safety Set - Subgroup 4: Patients who reported renal AEs or confirmed notable renal laboratory values in retrospective period.

Source: Appendix 1- ICL670AIT14-Tables and Figures document

CHMP comment

As requested, the MAH has provided figures with SCr changes (with percentage of change) compared to baseline at registration enrollment for each quarter in each safety subgroups 2, 3 and 4.

Unfortunately, such data are not available for CrCl changes. Subanalysis for adults and paediatric patients have been also provided.

In summary, in the 3 safety subgroups above, overall stability of SCr mean changes is observed with mean changes between -10% to +21% compared with mean baseline values in overall population. However, it seems that in sub group 2, mean SCr changes return to baseline (mean) values or even less (-10% to 0 % of changes), although in subgroups 3 and 4 (with renal AEs in registration studies or during the retrospective period); SCr mean changes is still around +10% compared with mean baseline values.

In the paediatric population, percentage of mean SCr changes is between 7 to 42% depending of subgroups but these figures should be taken with caution as the number of children is smaller compared with adults and SCr values could change with the physical development of children.

Issue partially addressed.

4- Of the 197 patients in safety subgroup 3, we do not known the percentage of patients taking deferasirox (monotherapy / sequential/concomitant) during the retrospective period. The MAH should clarify and discuss if any renal deterioration is observed in each subgroup taking deferasirox (monotherapy / sequential / concomitant) compared with baseline. A subanalysis for respectively for adults and paediatric patients should be also provided.

MAH's response

It should be emphasized again, that the focus of this study was to measure the long-term renal safety in patients on deferasirox therapy, regardless of exposure time and in real treatment practice. With the goal of the study to mimic real-life exposure, it was more clinically meaningful to observe these patients as a single group, where patients may have been on and off treatment and using iron chelators other than deferasirox, on and off both as single agents, or as combination therapy.

Over time, the patients in safety subgroup 3 (who reported renal adverse events (AEs) or confirmed notable renal values in the registration period) might have had periods of monotherapy, sequential therapy, and concomitant administration of deferasirox and other iron chelators, considering that treatments were as per physician prescription, and not on a specific schedule. None of the patients had only sequential therapy or concomitant therapy exclusively and there was no single treatment pattern over time. Thus, it is not possible to identify or differentiate patients as being in a single treatment group (monotherapy, sequential therapy, or concomitant therapy), especially in a way that would be clinically meaningful. It is known, however, that five patients were treated exclusively with deferasirox and no other iron chelators since enrollment in the registration studies (and not only in the retrospective period). For completeness, brief narratives of these patients and related renal events are presented below:

☐. The subject had participated in study CICL670A0105 and its extension, and had β –thalassemia major as underlying disease. Among the concomitant medications administered during the retrospective period, the subject was on enalapril maleate for hypertension between November 2007 and June 2010.

Six (6) renal adverse events were reported for this patient between October 2010 and February 2015: renal colic – right renal lithiasis, renal colic – right ureteral stone, 2 cases of renal colic and 2 cases of

nephrocalcinosis. All the events were mild in severity, none was suspected of being related to deferasirox and no particular action was required except for the use of concomitant medication in some cases. Serum creatinine values were stable over the retrospective period (Q1-Q30) and between 0.75-1 mg/dl. Creatinine clearance values were available only for Q28 (72 ml/min) and Q29 (91 ml/min). Urinary protein/creatinine ratios were also steady and between 0.08 and 0.35.

☐. The subject had participated in study CICL670A0108 and its extension and had myelodysplastic syndrome (MDS) as underlying disease. The subject was treated with lenalidomide and steroids for myelodysplastic syndrome and subsequently with thioguanine, cytarabine and hydroxyurea for progression of MDS to acute myeloid leukemia in March 2008. No iron chelation treatment was implemented during the retrospective period.

No renal adverse events were reported for this patient. Serum creatinine values were available only from Q1 to Q8 and were between 0.65 and 0.89 mg/dl. Creatinine clearance and urinary protein data were not available.

☐. The subject had participated in study CICL670A0108 and its extension, and had myelodysplastic syndrome secondary to non-Hodgkin's lymphoma (NHL) as underlying disease. NHL was treated first with vincristine and prednisone and subsequently with vinblastine, cyclophosphamide, doxorubicin and prednisone. The subject also took ramipril for hypertension and metildigoxin, amiodarone and carvedilol for atrial arrhythmia. Iron chelation treatments were not administered to this subject during the retrospective period.

The subject was hospitalized due to an increase of creatinine above the upper limit of normal. This serious adverse event (SAE) was considered resolved on 22 April 2005 and not related to deferasirox. Serum creatinine values were available only from Q1 to Q5 and were between 0.9 and 1.4 mg/dl. Creatinine clearance was 61 ml/min at Q1 and Q2, 41-42 ml/min at Q3 and Q4, and 64 ml/min at Q5. Urinary protein values were not available.

Note: This subject was diagnosed with non-Hodgkin's lymphoma in February 2005, started chemotherapy in April 2005 and died on 3 November from cardiac complications.

☐. The subject had participated in study CICL670A0108 and its extension and had myelodysplastic syndrome as underlying disease. The following concomitant medications were reported for this subject: eutirox for hypothyroidism, fosinopril for hypertension, clonazepam as antiepileptic, aspirin as antithrombotic agent and hydroxycarbamide for progression of MS. The subject did not take any iron chelators during the retrospective period.

No renal adverse events were reported for this subject and renal laboratory data were available only sporadically (Q1, Q8, Q10, Q12, Q14 and Q15). Serum creatinine was 0.6 - 1.0 mg/dl and only 4 values were available for creatinine clearance: 79.5 ml/min at Q1, 85.9 ml/min at Q8, 54.9 ml/min (below lower limit of normal) at Q12 and 39.1 ml/min (below lower limit of normal) at Q15. In the Investigator's judgment, the reductions in creatinine clearance were compatible with weight loss (from 63 to 46 kg). Urinary protein data were not available.

Note: this subject died on 19 August 2009 from progression of myelodysplastic syndrome in acute myeloid leukemia.

☐. The subject had participated in study CICL670A0105 and its extension and had β - thalassemia major as underlying disease. No adverse events were reported for this patient. Serum creatinine values were stable over the retrospective period (Q1-Q30) and between 0.55-0.9 mg/dl. Creatinine clearance and urinary protein values were not available.

CHMP comment

The MAH cannot provide the subanalysis requested. They have argued that the study focuses to "measure" the long-term renal safety in patients on deferasirox therapy, regardless of exposure time and in real treatment practice. Also, they cannot identify or differentiate patients as being in a single treatment group (monotherapy, sequential therapy, or concomitant therapy), especially in a way that would be clinically meaningful.

The deferasirox impact's on long term renal effects cannot be analysed accurately. Therefore, we consider that no reliable conclusion can be drawn from these descriptive data.

5- In the safety subgroup 4, a total of 87 patients (52.41% of subgroup 4) were affected by renal AEs in the retrospective period including 18 paediatric patients (<18 years-old). No details were provided on the nature of renal AEs in this subgroup. In addition a discrepancy was noted with table 14.3.1-6 where a total of 86 patients experienced renal AE (52.12%). The MAH should clarify.

MAH's response

Subgroup 4 (N=165) was made up of patients with reported renal AEs or confirmed notable renal laboratory values during the retrospective period. Eighty-six (86) of the 165 patients (52.12%) in subgroup 4 reported at least one renal adverse event during the retrospective period: 69 out of the 132 (52.27%) adult patients and 17 out of the 33 (51.52%) pediatric patients reported at least one renal AE. Table 2-1 shows the number of patients affected by renal adverse events by MedDRA System Organ Class (SOC) and Preferred Term (PT). Nephrolithiasis was the most common AE in both age groups and was reported in 18.94% (N=25) of patients aged 18 or older and in 18.18% (N=6) of patients under 18 years of age. Renal colics were the next most frequent event, espe cially among patients aged 18 or older [18.94% (N=25) in adults and 9.09% (N=3) in pediatric patients], followed by abnormal urine protein/creatinine ratios (4.55%, N=6 adults and 15.15%, N=5 under 18), increased urine protein/creatinine ratios (2.27%, N=3 adults and 6.06%, N=2 under 18) and increased blood creatinine (6.82%, N=9 adults and 6.06%, N=2 under 18).

Table 2-1 Renal adverse events by SOC and PT (Safety set – subgroup 4)

			Age <18 years (N=33)		Age ≥ 18 years (N=132)		Total (N=165)	
			N	%	N	%	N	%
	System Organ Class	Preferred Term						
Patients with Renal Adverse Events			17	51.52	69	52.27	86	52.12
Patients with Renal Adverse Events by SOC and PT	Infections and infestations	TOTAL by SOC	0	0	3	2.27	3	1.82
		Cystitis	0	0	2	1.52	2	1.21
		Urinary tract infection	0	0	1	0.76	1	0.61
	Investigations	TOTAL by SOC	9	27.27	20	15.15	29	17.58
		Blood creatinine abnormal	0	0	1	0.76	1	0.61
		Blood creatinine increased	2	6.06	9	6.82	11	6.67
		Protein urine present	0	0	3	2.27	3	1.82
		Urine protein/creatinine ratio abnormal	5	15.15	6	4.55	11	6.67
		Urine protein/creatinine ratio increased	2	6.06	3	2.27	5	3.03
		Urine sodium increased	0	0	1	0.76	1	0.61
	Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	TOTAL by SOC	0	0	1	0.76	1	0.61
		Angiomyolipoma	0	0	1	0.76	1	0.61
	Renal and urinary	TOTAL by SOC	13	39.39	53	40.15	66	40.00

	disorders	Acute kidney injury	0	0	1	0.76	1	0.61
		Bladder spasm	0	0	1	0.76	1	0.61
		Calculus ureteric	1	3.03	1	0.76	2	1.21
		Glycosuria	0	0	2	1.52	2	1.21
		Hematuria	1	3.03	0	0.00	1	0.61
		Hydronephrosis	0	0	4	3.03	4	2.42
		Hypocitraturia	0	0	1	0.76	1	0.61
		Nephrocalcinosis	2	6.06	5	3.79	7	4.24
		Nephrolithiasis	6	18.18	25	18.94	31	18.79
		Pollakiuria	0	0	1	0.76	1	0.61
		Proteinuria	2	6.06	8	6.06	10	6.06
		Pyelocaliectasis	0	0	2	1.52	2	1.21
		Renal colic	3	9.09	25	18.94	28	16.97
		Renal cyst	2	6.06	2	1.52	4	2.42
		Renal failure	0	0	1	0.76	1	0.61
		Renal glycosuria	0	0	1	0.76	1	0.61
		Renal tubular disorder	0	0	2	1.52	2	1.21
		Urethral stenosis	0	0	1	0.76	1	0.61
	Surgical and medical procedures	**TOTAL by SOC**	**1**	**3.03**	**0**	**0**	**1**	**0.61**
		Lithotripsy	1	3.03	0	0	1	0.61

A patient could report more than one Renal Adverse Event. Patients were counted only once in each row.
Only Renal Adverse Events reported in the retrospective period were considered.
Terms were codified with MedDRA dictionary, version 18.1.
Safety Set - Subgroup 4: Patients with renal AEs or confirmed notable renal laboratory values during the retrospective period.
Source: Appendix 1- ICL670AIT14-Tables and Figures document

CHMP comment

The MAH confirms the total number of 86 patients with at least one renal AE during the retrospective period. Details of renal events were provided: main renal events were nephrolithiasis, renal colic and UPCR abnormal or increased and SCr increased.

Clarifications have been given. Issue addressed.

6- It would be appreciated that the MAH performed a comprehensive safety analysis in the safety subgroup n°4 with a description of renal AEs and notable renal function parameters by type of patients (i.e patients on deferasirox only, on multiple chelators (by different combinations), other single chelators (deferoxamine, deferiprone). A subanalysis for respectively for adults and paediatric patients should be also provided.

MAH's response

As stated previously in the response to Question 4, the focus of this study was to measure the long-term renal safety in patients on deferasirox therapy, regardless of exposure time and in real treatment

practice. With the goal of the study to capture real-life exposure, it was more clinically meaningful to observe these patients as a single group, where patients may have been on and off treatment and using iron chelators other than deferasirox , on and off both as single agents, or as combination therapy.

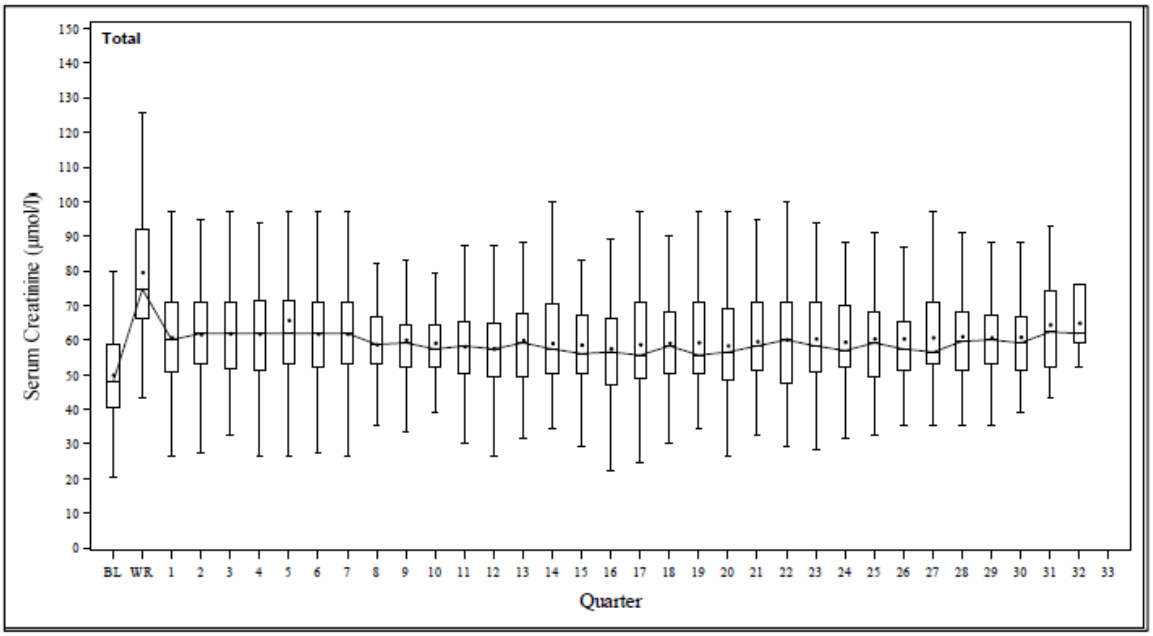
Over time, the patients in safety subgroup 4 (who reported renal adverse events (AEs) or confirmed notable renal values in the retrospective period) had periods of monotherapy, sequential therapy, and concomitant administration of deferasirox and other iron chelators. None of the patients had only sequential therapy or concomitant therapy exclusively, and there was no single treatment pattern over time. Thus, it is not possible to identify or differentiate patients as being in a single treatment group (monotherapy, sequential therapy, or concomitant therapy), especially in a way that would be clinically meaningful. It is known, however, that 98 patients were treated exclusively with deferasirox for various periods of time and no other iron chelators in the retrospective period. For completeness, a summary and analysis of these patients showing the percentage of serum creatinine (SCr) changes compared to baseline are presented below:

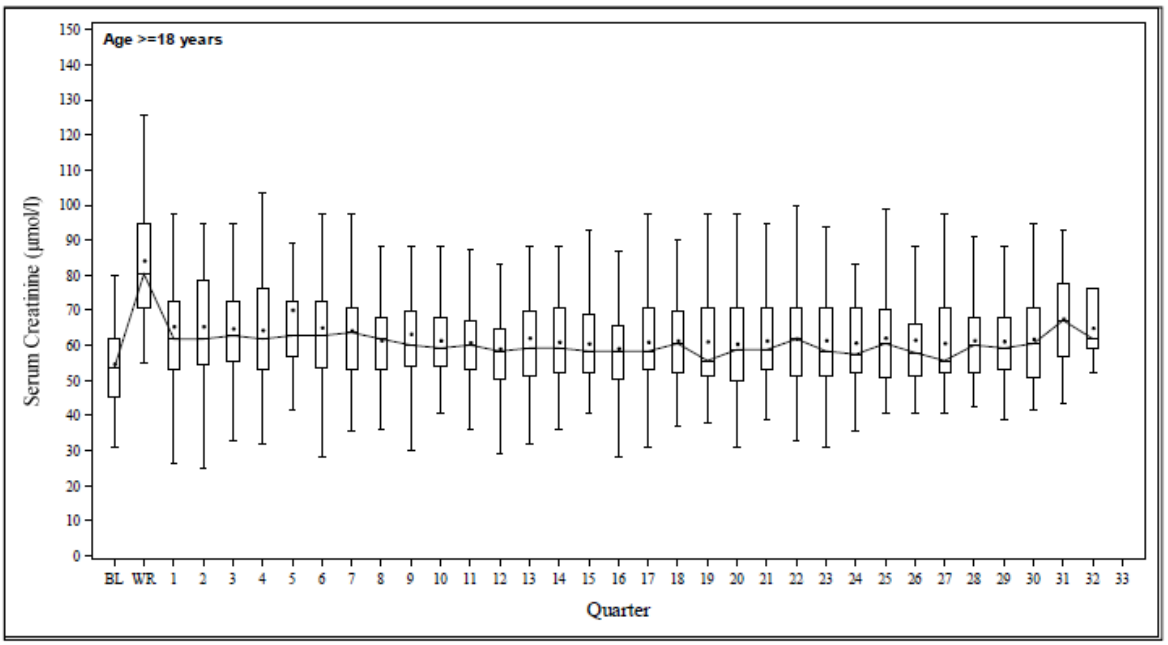
An additional analysis was performed to assess serum creatinine in patients (N=98) who took only deferasirox for iron chelation during the retrospective period. Seventy-one of these patients were adults, and 27 were under the age of 18 at Q1. Of note, patients ≥ 18 years had a mean treatment duration of 91.25 months with a mean dosage of 1443.12 mg, and patients <18 years were on treatment for a mean of 84.73 months with a mean dose of 1431.66 mg. Mean baseline SCr was 50.05 ± 13.69 µmol/L overall (range: 20.35 – 80.00), 54.79 ± 12.25 µmol/L in patients ≥ 18 years (range 30.95 – 80.00) and 37.57 ± 8.49 µmol/L in patients under ≤18 (range: 20.35 – 59.23). As shown in Figure 2-4, SCr values were stable throughout the retrospective period in the adult population and in mean between 60-65 µmol/L, corresponding to a 15-20% increase from baseline in most cases.

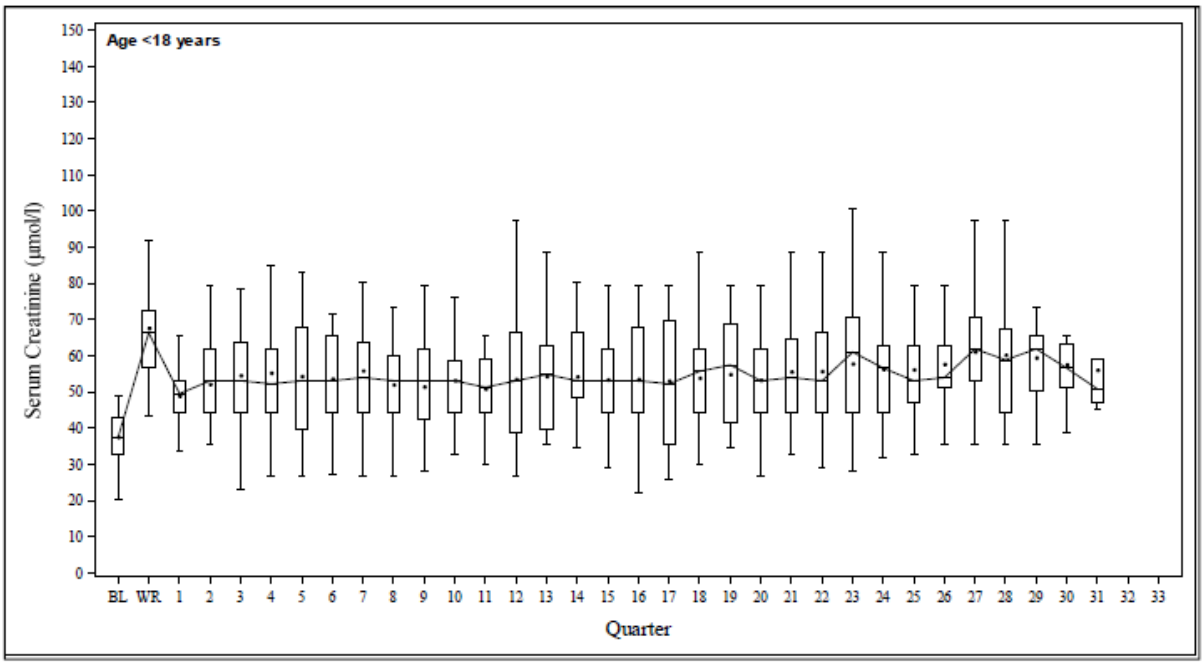
It should be noted the majority (71 of the 98 patients) in this overall subgroup were adults, and since the total is dominated by the larger adult subpopulation, the modest increase in >18 years between Q1 and Q30 is reflective of the age distribution and normal growth. Specifically, the median age of the 27 pediatric patients was 14 years at Q1, with a median age at the time of consensus of 21 years.

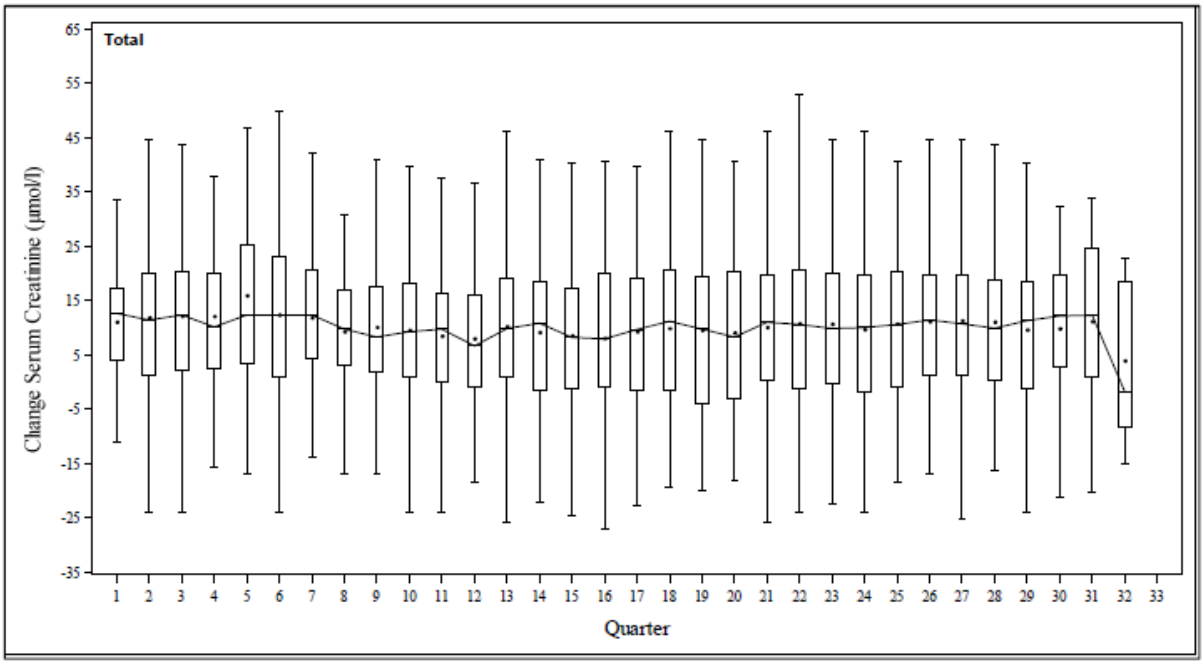
SCr was also quite constant in the pediatric population, with values between 50-55 µmol/L from Q1 to Q22 and between 55-60 µmol/L from Q23 to Q32. Compared to baseline, SCr values increased at Q1-Q23 and slightly more until Q32. The trend of SCr over time is comparable between subgroup 4 (patients with renal AE occurring during the retrospective study period) and subgroup 2 (patients talking chelators other than deferasirox). While a slightly higher absolute change of SCr from baseline can be observed in subgroup 4, absolute values of SCr in both subgroups remain generally within the limits of normal.

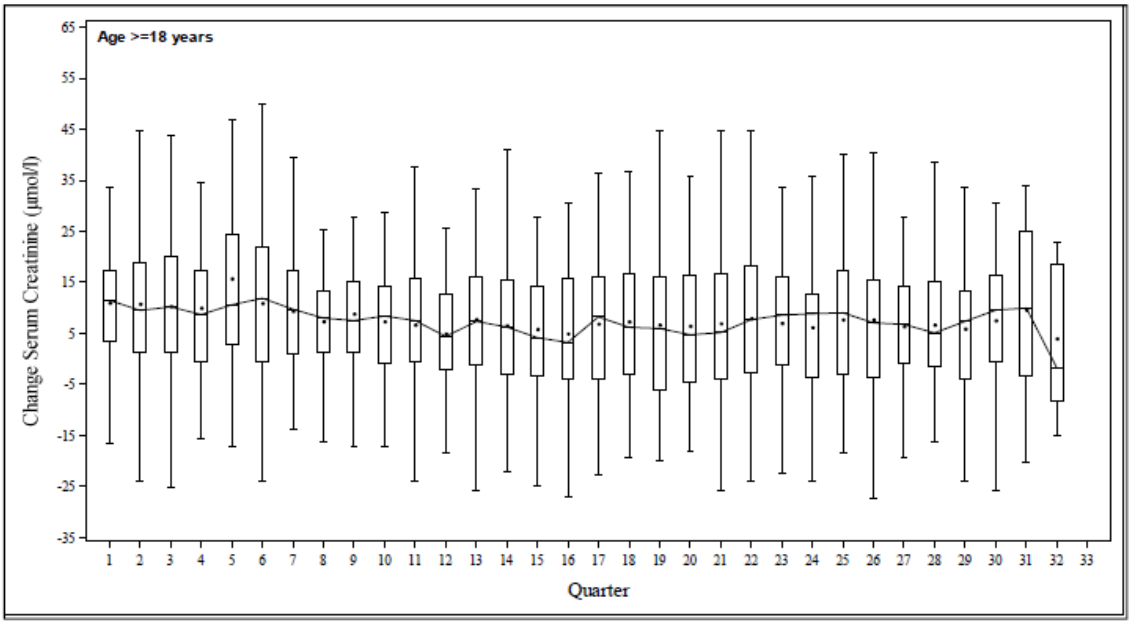
Figure 2-4 **Serum creatinine: graph by visit and change vs. baseline in the registration studies (Safety Set – Set of patients treated only with deferasirox in the retrospective period)**

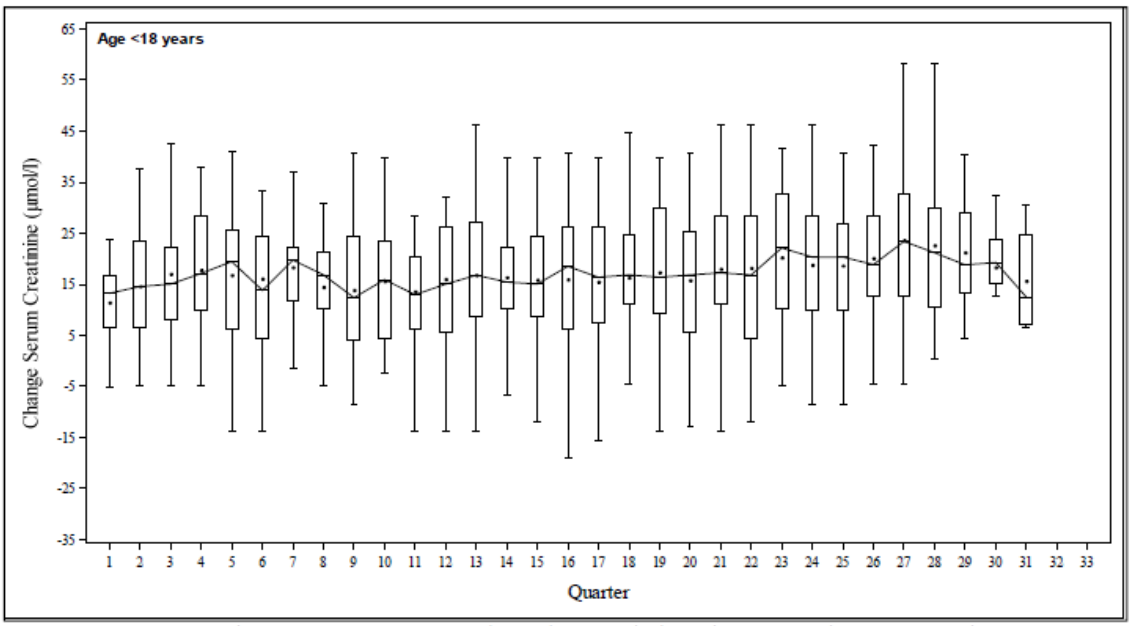





Age <18 years
Serum Creatinine (µmol/l)
Quarter
BL WR 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33


Total
Change Serum Creatinine (µmol/l)
Quarter
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33





Baseline (BL) and Worst (WR) values were collected in the registration studies, quarterly values in the retrospective period.
Worst values were the highest serum creatinine collected during the registration studies.
The markers inside the boxes indicate the mean values, the lines connect the median values over time. The length of the boxes represent the distance between Q1 (25th percentile) and Q3 (75th percentile); the whiskers represent the minimum values above 1.5 × IQR below Q1 and maximum values below 1.5 × IQR above Q3.
IQR is the interquartile range, i.e. the distance between Q1 and Q3
Source: Appendix 1- ICL670AIT14-Tables and Figures document

CHMP comment

The MAH cannot provide the subanalysis requested. They have argued that the study focuses to "measure" the long-term renal safety in patients on deferasirox therapy, regardless of exposure time and in real treatment practice. Also, they cannot identify or differentiate patients as being in a single

treatment group (monotherapy, sequential therapy, or concomitant therapy), especially in a way that would be clinically meaningful.

The MAH performed an additional analysis on SCr changes for 98 patients who were treated exclusively with deferasirox for various periods of time and no other iron chelators in the retrospective period. SCr values were stable throughout the retrospective period corresponding to a 15-20% increase from baseline in most cases.

The deferasirox impact's on long term renal effects cannot be analysed accurately. Therefore, we consider that no reliable conclusion can be drawn from these descriptive data.

7- The MAH should clarify the definition of "distinct renal AEs by LLT" and clarify what is the difference with the total number of renal AEs.

MAH's response

In this study, patients ≥ 18 reported a total of 164 AEs whereas patients <18 reported a total of 40 events. In this case, all the events were counted even if the same event occurred more than once in the same patient when they were younger than 18, and thereafter, when they were older than 18. These patients reported 110 vs. 27 different types of AEs by MedDRA low level term (LLT), respectively, and the numbers are lower than the ones expressed previously because each LLT is counted only once for each patient. Adult patients therefore reported both a greater number of events and a greater number of types of events.

CHMP comment

Clarifications have been given. Issue addressed.

6. Rapporteur's overall updated conclusion and recommendation

This study is a retrospective chart review of patients with transfusional hemosiderosis enrolled in the deferasirox registration studies (CICL670A0105,106,107,108 and 109) and were treated with at least one dose of DFX. The primary objective of this study was to evaluate the trend of serum creatinine over time in those patients. The long term renal safety is also one of this study's objectives.

We acknowledge that this retrospective chart review was a unique opportunity to collect historical data from patients enrolled in registration studies, especially as more than 90% of the population were observed for at least 7 years after completion of registration studies. However, interpretation of these data is difficult due to some limitations such as the nature "retrospective" and "descriptive" of the study, the lack of data available for key renal parameters such as UPCR and CrCl, the methodology used for treatment duration calculation. Also, data from safety set cannot allow to assess the role of deferasirox on the variation of renal parameters over time as patients received either multiple iron chelators (sequential/concomitantly) or other iron chelators (deferoxamine, deferiprone,..).

Also the main secondary objectives to evaluate renal function parameters in patients who had been treated with only deferasirox could not be reached due to the lack of patients in this subgroup (n=5).

The MAH reminded that the concept of this study would be to observe the long-term trends of overall renal function from patients charts of those who were enrolled into the deferasirox registration studies and it was recommended (in Apr 2014 after ANSM consultation meeting with the CHMP vice chairman) to include data from patients not treated with deferasirox during the retrospective period in order to differentiate disease from chelation effects. In real-life practice, patients are on iron chelation as a long-life, chronic therapy where treatment interruption are frequent and patients may be on and off treatment. Therefore, no accurate estimation of deferasirox exposure can be calculated.

As requested, the MAH performed an analysis of SCr mean change vs baseline value (instead of worst value). Despite an overall stability of mean SCr values, the mean SCR changes are between [-10% to +21%]. In sub group 2, mean SCr changes return to baseline (mean) values or even less (-10% to 0 % of changes), although in subgroups 3 and 4; SCr mean changes is still around +10% compared with mean baseline values.

According to the MAH, this study focuses to "measure" the long-term renal safety in patients on deferasirox therapy, regardless of exposure time and in real treatment practice. Also, they cannot identify or differentiate patients as being in a single treatment group (monotherapy, sequential therapy, or concomitant therapy), especially in a way that would be clinically meaningful.

The clarifications data provided by the MAH cannot allow to better characterize the impact of deferasirox therapy on the long term renal safety profile of these patients.

Therefore we maintain that no reliable conclusion could be drawn on the long term safety of deferasirox based on this study's results.

☒ **Fulfilled:**

No regulatory action required.