Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: A Pooled Analysis of Pediatric Clinical Trial Data

Date:	April 9, 2018
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Drug Name(s):	Exjade® (deferasirox) Tablets for Oral Suspension Jadenu® (deferasirox) Film Coated Tablets Jadenu® (deferasirox) Sprinkles
Subject	Pooled analysis of deferasirox pediatric clinical trial data
Application Type/Number:	NDA 021882 NDA 206910 NDA 207968
Applicant/sponsor:	Novartis
OSE RCM #:	2015-2509
TSI #:	TSI 1682

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EXECUTIVE SUMMARY

This review follows a consult from the Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products (DHP) to address a request from the chairman of the Pediatric Advisory Committee (PAC), regarding the safe use of deferasirox in young children due to concerns about a fatal case report. A Tracked Safety Issue (TSI) was created in April 2016 and a multi-disciplinary study team was formed. Exjade is an orally active iron chelator which was approved in 2005 for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older. A Boxed Warning was added in 2010 which recommends close patient monitoring, including laboratory tests of renal and hepatic function. In 2015 FDA approved Jadenu (deferasirox) tablets, a new formulation of deferasirox, for the same indications as Exjade. Serious and fatal cases of deferasirox-induced multi-organ toxicity in young children have been published, and have also been received through FDA's Adverse Event Reporting System (FAERS). Clinical features of these cases suggest that lower body iron burden, higher deferasirox dose, or an interaction between these two factors, can increase the risk of serious toxicity. In preclinical studies with deferasirox, juvenile animal models with relatively lower body iron burdens developed more severe kidney injury. An analysis of the relationship between estimated glomerular filtration rate (eGFR) and dose-normalized drug exposure in pediatric patients was conducted by FDA Clinical Pharmacology reviewers. The change in deferasirox plasma concentration (Cmin) in relation to eGFR was estimated using a linear mixed effect model. Results showed that for a 25% decrease in eGFR (from 120 ml/min/1.73m^2 to 90 ml/min/1.73m^2), a 21% increase in Cmin is predicted. This suggests that, despite eGFR within normal limits, small decreases in eGFR could lead to significant increases in drug exposure, creating a vicious cycle that could lead to severe toxicity.

The purpose of this current review is to identify risk factors for acute kidney injury (AKI) in pediatric patients treated with deferasirox to inform product labeling, and provide specific information to promote safe use of deferasirox in children. Three analyses were conducted or reviewed by the TSI study team utilizing pooled pediatric clinical trial datasets provided by the sponsor in response to FDA information requests.

The goals of these analyses are:

- To investigate whether relatively higher doses of deferasirox and/or relatively lower body iron burden (indicated by serum ferritin level), together or independently, increase the risk for AKI in children with transfusion-dependent thalassemia.
- To determine whether exposure-adjusted incidence rates of clinical adverse events are higher in children participating in deferasirox clinical trials during periods when serum ferritin is relatively low, and deferasirox dose is relatively high at the same time.
- To assess the risk of AKI in Study CICL670A2411, a 5-year registry in children age 2 to <6 years at study entry, based on clinical laboratory data collected during the study.

A nested case control analysis was conducted within a deferasirox pediatric pooled clinical trial dataset to evaluate the effects of dose and serum ferritin level, separately and combined, on kidney function. Among 1213 children (aged 2 to 15 years) with transfusion-dependent thalassemia, 162 cases of AKI (eGFR ≤90 ml/min/1.73m2) and 621 matched-controls with normal kidney function (eGFR ≥120 ml/min/1.73m^2) were identified. The primary findings were:

- A 26% increased risk of AKI was observed with each 5 mg/kg increase in daily deferasirox dosage starting at 20 mg/kg/day (95% CI: 1.08-1.48)

- A 25% increased risk for AKI was observed with each 250 mcg/L decrease in serum ferritin starting at 1250 mcg/L (95% CI: 1.01-1.56).
- Among pediatric patients with a serum ferritin <1000 mcg/L, those who received deferasirox dosage >30 mg/kg/day, compared to those who received lower dosages, had a 4.5-fold higher risk for AKI (95% CI: 1.25-15.95), consistent with overchelation.

A cohort based analysis of adverse events was conducted in the pooled clinical trial data submitted by the sponsor. Pediatric patients who received deferasirox dose >25 mg/kg/day when their serum ferritin was <1000 mcg/L (n=158) had a 6-fold greater rate of renal adverse events (95% CI: 1.75-21.36) and a 2-fold greater rate of dose interruptions (95% CI: 1.33-3.17) compared to the time-period prior to meeting these simultaneous criteria. Adverse events of special interest (as defined by the sponsor) occurred 1.9-fold more frequently when these simultaneous criteria for dose and serum ferritin were met, compared to preceding time-periods (95% CI: 1.05-3.48).

An analysis of clinical laboratory data was conducted to assess decreases in eGFR in Study CICL670A2411, a 5-year registry in children age 2 to <6 years at study entry. Serum creatinine was measured monthly in most patients; however, many study sites evaluated serum creatinine results using reference ranges that may not have been age-appropriate. The sponsor was asked to provide a dataset with eGFR values from the registry calculated using the appropriate Schwartz equations. Of the 267 pediatric patients enrolled in the 5-year registry, 242 patients had pre- and post-baseline eGFR measurements. Of these, 116 (48%) patients had a decrease in eGFR of ≥33% observed at least once. Twenty-one (18%) of these 116 patients with decreased eGFR had a dose interruption, and 15 (13%) of these 116 patients had a dose decrease within 30 days. This analysis showed that AKI that could cause increased deferasirox levels and potential exposure-related toxicity occurred commonly in young children participating in Study CICL670A2411, and often was followed by a dose decrease or interruption of therapy.

Results of the nested case-control study of pooled clinical trial data in pediatric transfusion-dependent thalassemia patients receiving deferasirox confirm that risk of AKI is markedly elevated when the dose of deferasirox is high compared to the body iron burden, as represented by serum ferritin levels. Use of high-dose deferasirox with lower serum ferritin levels was associated with a higher risk of AKI than either high dosage or low ferritin alone, consistent with overchelation as a causative factor. A similar clinical pattern was observed in an analysis of clinical adverse events in the pooled clinical trial dataset, and was notable for an increased risk of renal adverse events, adverse events of special interest (as defined by the sponsor), and the occurrence of therapy interruptions. These findings highlight the importance of clinical laboratory monitoring to identify relatively lower levels of body iron burden in children taking deferasirox. AKI risk may be mitigated by using the lowest possible dose to establish and maintain an acceptable level of body iron burden. Deferasirox therapy should be interrupted or discontinued in children with evidence of AKI, and during acute illnesses, or other conditions which may predispose to volume depletion to avoid severe toxicity. We recommend addition of the results of these safety analyses to the product labeling for Exjade, as well as similar language for Jadenu (for an equivalent deferasirox dose).

1 INTRODUCTION

1.1 BACKGROUND

This review follows a consult from the Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products (DHP) to address a request for safety analyses from the chairman of the Pediatric Advisory Committee (PAC), after the mother of a young transfusion-dependent thalassemia patient spoke during the public session of a PAC in September 2015 and told the story of how her daughter passed away unexpectedly while taking Exjade (deferasirox). Initially, FDA asked the sponsor to conduct a pooled analysis of children participating in Exjade clinical trials to evaluate clinical outcomes after fever or dehydration adverse events (AEs) and to determine whether interruption of deferasirox therapy was influential and helpful in avoiding adverse effects.[1] Seventeen (17) studies with a total of 1844 patients (ages 2 to 15 years) were identified. However, the results of the analysis were not considered to be conclusive by the FDA review team. A Tracked Safety Issue (TSI) was created in April 2016 and a multi-disciplinary study team was formed to conduct additional analyses of the pooled clinical trial data provided by the sponsor.

1.2 REGULATORY HISTORY

Exjade is an orally active iron chelator which was approved in 2005 for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older. A Boxed Warning was added in 2010 which warns of renal impairment, hepatic impairment, and gastrointestinal hemorrhage with the use of Exjade. The Boxed Warning also reminds health care practitioners of the need for close patient monitoring, including laboratory tests of renal and hepatic function. In 2015 FDA approved Jadenu (deferasirox) tablets, a new formulation of deferasirox, for the same indications as Exjade.

1.3 CRITICAL KNOWLEDGE GAPS ADDRESSED IN THIS REVIEW

In addition to the index case described above, serious and fatal cases of deferasirox-induced multi-organ toxicity in young children have been published,[2,3] and have also been received through FDA's Adverse Event Reporting System.[4] Clinical features of these cases suggest that lower body iron burden (indicated by serum ferritin levels), higher deferasirox dose, or an

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[1] NDA 21-882 Exjade® (deferasirox) Tablets. Novartis Response (dated 2/22/16) to FDA Information Request (dated 1/21/16).

[2] Ramaswami A, Rosen DJ, Chu J, Wistinghausen B, Arnon R. Fulminant Liver Failure in a Child With β-Thalassemia on Deferasirox: A Case Report. J Pediatr Hematol Oncol. 2017 Apr;39(3):235-237.

[3] Marano M, Bottaro G, Goffredo B, Stoppa F, Pisani M, Marinaro AM, Deodato F, Dionisi-Vici C, Clementi E, Falvella FS. Deferasirox-induced serious adverse reaction in a pediatric patient: pharmacokinetic and pharmacogenetic analysis. Eur J Clin Pharmacol. 2016 Feb;72(2):247-8.

[4] Deferasirox (Exjade NDA 021882; Jadenu NDA 206910) Pharmacovigilance Review; TSI 1682; OSE RCM #2015-2509; DARRTS ID 4078289; dated March 31, 2017.

interaction between these two factors, can increase the risk of serious multi-organ toxicity including acute kidney injury (AKI) and severe liver injury in pediatric patients.

Dose-related kidney injury associated with deferasirox is generally reversible when therapy is interrupted or discontinued.[5,6,7] However, in preclinical studies with deferasirox, juvenile animal models with relatively lower body iron burdens developed more severe kidney injury.[8] Based on these findings, investigation of the possible increased susceptibility of young children to AKI was conducted under the TSI. An analysis of the relationship between estimated glomerular filtration rate (eGFR) and dose-normalized drug exposure in pediatric patients was conducted by FDA Clinical Pharmacology reviewers using data from three deferasirox clinical studies (CICL670A2409, CICL670A0107, and CICL670A2201).[9] The change in deferasirox minimum (trough) plasma concentration (Cmin) in relation to eGFR was estimated using a linear mixed effect model. The FDA reviewer found that for a 25% decrease in eGFR (from 120 ml/min/1.73m^2 to 90 ml/min/1.73m^2), a 21% increase in Cmin is predicted by these data. This suggests that, despite eGFR within normal limits (> 90 mL/min/1.73m^2 per FDA Guidance criteria), small decreases in eGFR could lead to significant increases in drug exposure, creating a vicious cycle that could cause severe toxicity.[10]

The purpose of this current review is to identify risk factors for acute kidney injury in children treated with deferasirox that can inform product labeling, and provide prescribers with specific information to promote safe use of deferasirox in children.

Three analyses were conducted by the TSI study team utilizing the pooled pediatric clinical trial datasets provided by the sponsor in response to FDA information requests. The goals of these analyses are:

- To investigate whether relatively higher doses of deferasirox and/or relatively lower body iron burden (indicated by serum ferritin level), together or independently, increase the risk for acute kidney injury in children with transfusion-dependent thalassemia.

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[5] Saliba AN, El Rassi F, Taher AT. Clinical monitoring and management of complications related to chelation therapy in patients with β-thalassemia. Expert Rev Hematol. 2016;9(2):151-68.

[6] Dubourg L, Laurain C, Ranchin B, Pondarré C, Hadj-Aïssa A, Sigaudo-Roussel D, Cochat P. Deferasirox-induced renal impairment in children: an increasing concern for pediatricians. Pediatr Nephrol. 2012 Nov;27(11):2115-2122.

[7] Bollig C, Schell LK, Rücker G, Allert R, Motschall E, Niemeyer CM, Bassler D, Meerpohl JJ. Deferasirox for managing iron overload in people with thalassaemia. Cochrane Database Syst Rev. 2017 Aug 15;8:CD007476.

[8] Nick H, Wong A, Acklin P, Faller B, Jin Y, Lattmann R, Sergejew T, Hauffe S, Thomas H, Schnebli HP. ICL670A: preclinical profile. Adv Exp Med Biol. 2002;509:185-203.

[9] NDA 21-882 Exjade® (deferasirox) Tablets. Novartis Response (dated 2/28/17) to FDA Information Request (dated 11/17/16).

[10] Deferasirox (Exjade NDA 021882; Jadenu NDA 206910) Office of Clinical Pharmacology Review; Safety-001682; Primary reviewer, Olanrewaju Okusanya, PharmD, MS; DARRTS ID 4193690; dated December 12, 2017.

- To determine whether exposure-adjusted incidence rates of clinical adverse events are higher in children participating in deferasirox clinical trials during periods when serum ferritin is relatively low, and deferasirox dose is relatively high at the same time.
- To assess the risk of acute kidney injury in Study 2411, a 5-year registry in children age 2 to <6 years at study entry based on clinical laboratory data collected during the study.

2 REVIEW METHODS AND MATERIALS

2.1 DOCUMENTS CONSIDERED FOR THIS REVIEW

- Novartis 2-Feb-2018 (NDA 21882, Seq #0235) response to the FDA information request dated 19-Jan-2018
- Novartis 21-Dec-2017 (NDA 21882, Seq #0234) response to the FDA information request dated 11-Dec-2017
- Novartis 22-Aug-2017 response (NDA 21882, Seq #0224, includes datasets) to the FDA information requests dated 7-Jul-2017 and 20-Jul-2017
- Novartis 22-May-2017 response (NDA 21882, Seq #0217, includes datasets) to the FDA information request dated 18-Apr-2017
- Novartis 1-Mar-2017 (NDA 21882, Seq #0215) response to the FDA information request dated 17-Nov-2016 (Clinical Pharmacology)
- Novartis 17-Nov-2016 (NDA 21882, Seq #0211, includes datasets) response to the FDA information request dated 20-Oct-2016
- Novartis 30-Aug-2016 (NDA 21882, Seq #0207, questions #1-2), 14-Sep-2016 (Seq #0208, questions #9-11, includes datasets), 27-Sep-2016 (Seq #0209, questions #3-4), and 4-Nov-2016 (Seq #0210, question #5) responses to the FDA information request dated 12-Aug-2016 (included multiple questions)
- Novartis 22-Jul-2016 (Seq 0205, includes datasets) response to the FDA information request dated 1-Jul-2016

2.2 ANALYTIC APPROACHES USED FOR THIS REVIEW

From the pool of 17 clinical studies included in the sponsor's initial safety analysis of fever and dehydration-related adverse events, [11] ten studies were identified by the sponsor which included transfusion-dependent thalassemia patients and adequate serum ferritin data to conduct an additional safety analysis of patients who received relatively high doses of deferasirox when serum ferritin levels were relatively low (e.g. < 1000 mcg/L).[12] To achieve the review objectives, three separate analyses were conducted of the pediatric clinical trial data submitted by the sponsor:

Study population – pooled dataset: - pediatric transfusion-dependent thalassemia patients (age 2-15 years) participating in deferasirox clinical trials (trials listed in Appendix 1)

1. Analysis of clinical laboratory data from pooled clinical trials using a nested case control study design to compare cases of acute kidney injury with normal controls

[11] Novartis Response submitted to NDA 021882 on 23-Feb-2016 (seq. no. 0201)

[12] Novartis 22-Aug-2017 response (NDA 21882, Seq #0224, includes datasets) to the FDA information requests dated 7-Jul-2017 and 20-Jul-2017.

2. Analysis of clinical adverse events from the pooled clinical trials comparing exposure-adjusted incidence rates of AEs during periods when dose was >25 mg/kg/day and serum ferritin was <1000 mcg/L, with periods before those simultaneous criteria were met, and with patients who did not meet the simultaneous criteria of dose >25 mg/kg/day and serum ferritin <1000 mcg/L.

Study population – pediatric patients with transfusional hemosiderosis age 2 - <6 years at study entry enrolled in the 5-year Pediatric Registry (n=261)

3. Analysis of clinical laboratory data from Study CICL670A2411 to evaluate changes in eGFR that may be indicative of acute kidney injury

3 NESTED CASE-CONTROL ANALYSIS OF LABORATORY DATA FROM POOLED CLINICAL TRIALS

3.1 STUDY OBJECTIVES

The primary objective of this nested case-control study is to investigate the effect of deferasirox dose and serum ferritin on acute kidney injury (AKI), and the possible interactions between the two risk factors. The primary outcome (AKI) is defined by baseline and follow-up eGFR values. Co-variates include patient age (within 1 year), gender, time since deferasirox initiation (within 1 month), and study site (matching).

3.2 METHODS

3.2.1 Clinical Trials Dataset

Ten (10) studies were identified which included transfusion-dependent thalassemia patients and provided adequate serum ferritin data to conduct the requested analyses. Complete datasets were provided by the sponsor.[13] Demographic variables included baseline age, baseline age-group (2-6 and 7-15 years), gender, race, study number, and study site. Dosage was recorded in mg/kg/day throughout the trials, notating dosage increases and decreases as well as dose interruptions and discontinuation of therapy. All laboratory values for renal function and ferritin were recorded during follow-up and were obtained at monthly intervals in most trials.

3.2.2 Cohort Formation

Within the clinical trials dataset, we created a nested cohort of study visits eligible for case and control selection. We allowed patients 2 to 15 years of age at the time of study enrollment with a diagnosis of transfusion-dependent thalassemia to contribute visits to our analysis. Each included patient was required to have a baseline visit and at least one follow-up visit where eGFR, deferasirox dosage, and serum ferritin levels were available. Assigning the visit as the subject for analysis ensured that each case and control would have recorded values for the study outcome and exposures of interest on the day of matching. A nested case-control study

[13] NDA 21-882 Exjade® (deferasirox) Tablets. Novartis Response (dated 8/18/17) to FDA Information Requests (dated 7/7/17 and 7/20/17).

was nested within our cohort, and this design was selected to ensure complete capture of exposure and outcome variables at the time of analysis, while also matching on duration of therapy.

3.2.3 Kidney Injury Cases

3.2.3.1 Primary analysis

Estimated glomerular filtration rate (eGFR) was chosen to define kidney injury because it is a widely-used measure of kidney function[14] and can provide a useful indicator of kidney function over time when measured sequentially, as in clinical trials.[15] The eGFR value is derived from the patient's serum creatinine measurement at each study visit.[16] The creatinine-based Schwartz formulas (the original Schwarz and modified [or bedside] Schwarz), were chosen for estimating GFR as these prediction formulas have been validated in pediatric patients. The original Schwarz formula was used when serum creatinine was assayed using the Jaffe method and the modified Schwarz formula was used when serum creatinine was assayed by enzymatic methods.[17]

Acute kidney injury (AKI) was identified during deferasirox therapy, and up to 14 days after therapy discontinuation, when additional follow-up was available, to avoid exclusion of events that resulted in cessation of drug therapy. We defined AKI by comparing a patient's eGFR value at each study visit to a threshold value or as the change from baseline eGFR, as follows. Patients with a baseline eGFR ≥100 mL/min/1.73m^2 were considered to have an episode of AKI during a study visit with eGFR ≤90 mL/min/1.73m^2. Patients with a baseline eGFR <100 mL/min/1.73m^2 were considered to have an episode of AKI during a study visit with an eGFR decrease from baseline ≥25% or an eGFR value ≤60mL/min/1.73m^2, whichever was higher. The first visit meeting these criteria was defined as the case visit, and each patient could contribute only one case to the analysis.

3.2.3.2 Secondary analysis

Children with transfusion-dependent thalassemia may appear to have a high glomerular filtration rate due to lower than average levels of serum creatinine. This may be due to an interplay of factors associated with chronic anemia, including lower muscle mass. Because this may impact the clinically relevant threshold eGFR for AKI in children with transfusion-dependent thalassemia, we varied our outcome definition in two sensitivity analyses to define AKI using thresholds of: 1) an eGFR <80 mL/min/1.73m^2 and, 2) an eGFR <100 mL/min/1.73m^2. In the

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[14] Filler G, Lee M. Educational review: measurement of GFR in special populations. Pediatr Nephrol. 2017 Dec 7.

[15] Pediatric Review. Division of Pediatric and Maternal Health (DPMH). Exjade (deferasirox) TSI 1682; Primary reviewer, Mona Khurana, MD; DARRTS ID 4036409; dated January 4, 2017.

[16] Wong CS, Warady BA, Srivastava T. Clinical presentation and evaluation of chronic kidney disease in children. In: UpToDate, Kim MS (Ed), UpToDate, Waltham, MA, 2017.

[17] Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009 Mar; 20(3):629-37.

presence of a true association between deferasirox dose or serum ferritin on AKI, we would expect the observed risk estimates to increase with greater severity of kidney injury, in the presence of widened confidence intervals due to decreased study power.

3.2.4 Pool of Eligible Controls for Matching

The pool of controls available for matching consisted of all patient visits with an eGFR ≥120mL/min/1.73m^2 at the time of the study visit. A patient could contribute multiple control visits for matching, but each visit could only be matched to a single case. Control visits were matched on age at visit (±1 year), gender (exact), time since drug initiation (±1 month) and study site. Inclusion of time since therapy initiation as a matching criterion allowed incidence density sampling within a specified range to account for expected deviation in the timing of visits among patients. Controls were selected to achieve a match of 4 control visits per case visit. [18]

3.2.5 Model Parameters

Deferasirox dosage in mg/kg/day was recorded in treatment intervals throughout follow-up. High-dose deferasirox was defined using two cutoffs, >25mg/kg/day and >30mg/kg/day, measured as the highest dose recorded at the time of a case or control visit or anytime in the prior 14 days. We allowed a two-week timeframe for detection of high dosage deferasirox as 1) a plausible window by which the presence of high-dose deferasirox could lead to the recorded kidney injury and 2) to correctly attribute a kidney injury to high-dose deferasirox in the presence of a recent dose change where nephrotoxicity was suspected but not yet laboratory confirmed.

Serum ferritin was measured as the lowest value recorded at the time of the case or control visit or anytime in the prior 14 days. Low serum ferritin was defined as a laboratory value <1000 mcg/L, and this definition was varied in 250 mcg/L decrements from <1250 mcg/L to <750 mcg/L. Baseline age was determined as the number of days between a patient's date of birth and the date of the baseline visit. Gender, study site, and baseline eGFR were also identified from clinical trial datasets.

3.2.6 Statistical Analysis

Conditional Logistic Regression was used to compute odds ratios (OR) and 95 percent confidence intervals (95%CI) to assess the association between high-dose deferasirox and/or low serum ferritin and the outcome of acute kidney injury. Our incidence density based sampling approach from a nested new-user exposure cohort allowed for the close approximation of the Odds Ratio to the Incidence Rate Ratio (RR).[19] Our primary model included dosage and serum ferritin as continuous variables. Dosage was defined in 5mg/kg/day increments starting at 20 mg/kg/day, while serum ferritin was defined in 250 mcg/L decrements starting at 1250 mcg/L. Clinically informed cut points for dosage (>25 mg/kg/day and >30

[18] Bergstralh EJ, Kosanke JL. Computerized matching of controls. Section of Biostatistics Technical report 56. 1995. Mayo Foundation. Accessed 4 April 2018. Available at < http://www.mayo.edu/research/departments-divisions/department-health-sciences-research/division-biomedical-statistics-informatics/software/locally-written-sas-macros>.

[19] Rodrigues L, Kirkwood BR. Case-control designs in the study of common disease: updates on the demise of the rare disease assumption and the choice of sampling scheme for control. Int J Epidemiol 1990;19(1):205-213

mg/kg/day) and for serum ferritin (<750 mcg/L, <1000 mcg/L, and <1250 mcg/L) were also assessed to inform recommendations for specific maximum deferasirox and serum ferritin values associated with increased risk for AKI. Additionally, the main effects for high-dose deferasirox (>30 mg/kg/day) and low serum ferritin (<1000 mcg/L), and their interaction, were assessed using the same statistical model. Here, the interaction term quantifies the presence of an excess (or reduced) risk beyond the combination of individual effects from both parameters. The odds ratio for acute kidney injury with each combination of dosage and serum ferritin values was calculated using the log odds of the parameter estimates and the interaction term. All analyses were performed using Statistical Analysis Software (SAS) version 9.4 (Cary, NC) and were verified by two data analysts on the FDA study team (RS and FT).

3.3 RESULTS

A total of ten clinical trials were identified which included children 2-15 years of age with transfusion-dependent thalassemia and which captured adequate pre- and post-baseline measurements of serum creatinine and serum ferritin for the analysis. Three of the studies (CICL670F2201, CICL670A0108, CICL670A2214) were very small and did not identify any cases. A description of the ten clinical trials, including the study number, study title, and study type (interventional versus observational) is provided in Appendix 1.

A total of 162 AKI cases from seven studies were identified in our primary analysis. Matching produced 621 control visits with normal renal function. A depiction of case and control selection is shown in Appendix 2. A description of study subject characteristics at baseline is shown in Appendix 3 for AKI cases and matched control visits. No statistically significant differences among cases and control visits were observed among covariates included in matching.

The primary analysis found a 26% increased risk of AKI with each 5 mg/kg increment in daily deferasirox dosage ($p<0.01$). AKI risk increased with progressively higher doses of >25 mg/kg/day (OR=1.40, p=0.1) and >30 mg/kg/day (OR=1.72, p=0.01).

While risk at a dosage cutoff of >25mg/kg/day was not significant in our primary analysis (eGFR≤90 ml/min/1.73m^2), a secondary case criteria defining AKI as an eGFR ≤100ml/min/1.73m^2 did observe significantly increased risk at this threshold dosage [RR 1.44, p=0.02]. Risk for AKI was significantly increased in all analyses for patients receiving a deferasirox dose >30mg/kg/day, compared to lower doses. The risk estimate increased as the severity of kidney injury worsened from eGFR ≤100 ml/min/1.73m^2 [RR=1.54, p=0.01] to eGFR ≤90 ml/min/1.73m^2 [RR=1.72, p=0.01] to eGFR ≤80 ml/min/1.73m^2 [RR=2.01, p=0.02] (Appendix 4).

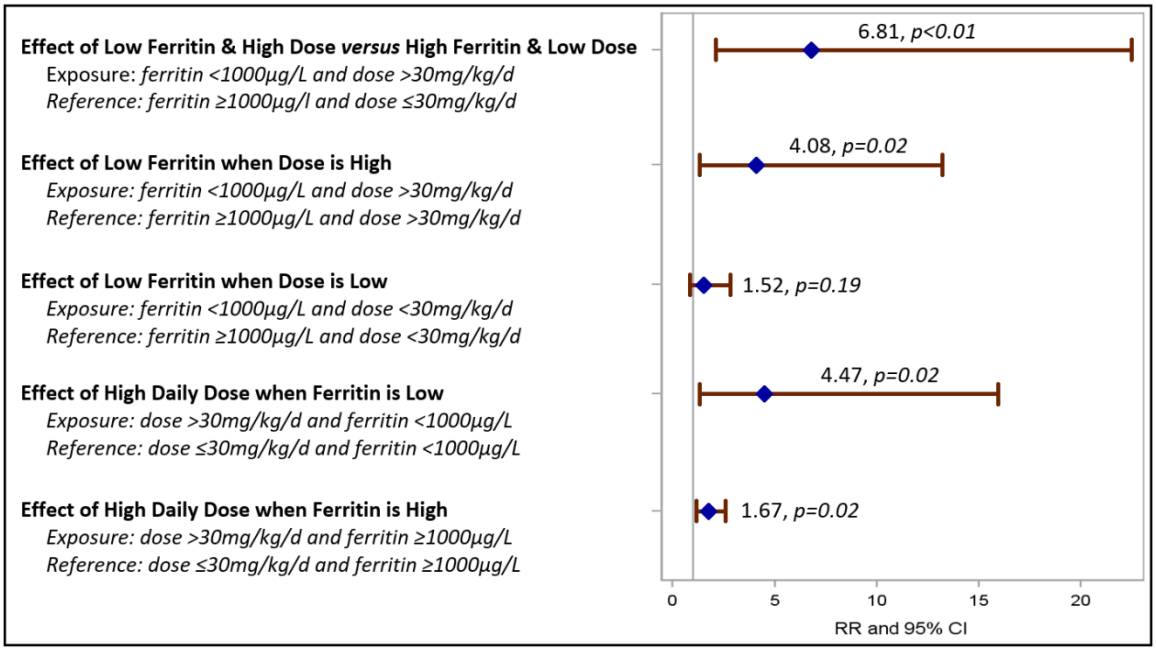
A 25% increased risk for AKI (p=0.04) was observed per 250 mcg/L decrease in serum ferritin starting at a threshold of 1250 mcg/L, when adjusting for the dose effect at 30 mg/kg/day. At specific serum ferritin levels, AKI risk was as follows: <1250 mcg/L [OR=1.40, p=0.17], <1000 mcg/L [OR=1.85, p=0.02], and <750 mcg/L [OR=2.01, p=0.06] (Appendix 5).

High-dose deferasirox (>30 mg/kg/day) was associated with a 1.7-fold (p=0.02) increased risk for AKI in children when serum ferritin was ≥1000 mcg/L and a 4.5-fold (p=0.02) increased risk when serum ferritin was <1000 mcg/L. Among children with a low serum ferritin (<1000 mcg/L), a 4.5-fold (p=0.02) increased risk for AKI was observed with high-dose deferasirox (>30 mg/kg/day), but not with lower deferasirox dose (<30mg/kg/day) [RR 1.52, p=0.19].

Notably, receipt of deferasirox dose >30mg/kg/day when serum ferritin was <1000 mcg/L resulted in a 6.8-fold (p<0.01) increased risk for AKI compared to children receiving deferasirox dose ≤30 mg/kg/day when serum ferritin was ≥1000 mcg/L (Figure 1 below, and Appendix 5 table).

The RR for the interaction term between high-dose deferasirox and low serum ferritin was 0.99 (0.67-2.15). This interaction term implies the two effects under investigation are additive, meaning that the total risk for AKI with deferasirox is the aggregate summation of risk for both high dosage and low serum ferritin.

Figure 1: Forest Plot for the combined effect of deferasirox dosage >30mg/kg/d and serum ferritin <1000 g/L on risk for AKI



3.4 CONCLUSION

This nested case-control analysis of clinical laboratory data from pooled clinical trials in children with transfusion-dependent thalassemia identified a trend toward increased risk for AKI with both higher deferasirox dose and lower serum ferritin. Use of high-dose deferasirox with lower serum ferritin levels was associated with a higher risk of AKI than either high dosage or low ferritin alone, consistent with overchelation as a causative factor. This finding highlights the importance of clinical laboratory monitoring to identify relatively lower levels of body iron burden in children taking deferasirox. AKI risk may be mitigated by using the lowest possible dose to establish and maintain an acceptable level of body iron burden. Deferasirox therapy should be interrupted or discontinued in children with evidence of AKI.

4 EXPOSURE-ADJUSTED INCIDENCE RATES OF ADVERSE EVENTS FROM POOLED CLINICAL TRIALS

At the request of FDA, the sponsor constructed a pooled clinical trial dataset and identified patients with transfusion-dependent thalassemia who received deferasirox doses > 25 mg/kg/day when their serum ferritin was < 1000 mcg/L.[20] Clinical and laboratory adverse events (AEs) with onset during the first period when patient dose was >25 mg/kg/day and serum ferritin was <1000 mcg/L, concurrently (referred to in this review as "simultaneous criteria" or "SC") were identified by the sponsor. Adverse Events of Special Interest (AESIs) were defined by the sponsor and included the following group terms: "gastrointestinal haemorrhage and ulcers"; "oesophagitis"; "hearing loss"; "increased liver transaminases"; "lens opacities", "retinal changes and optic neuritis"; "peripheral blood cytopenias"; "renal disorders"; "severe cutaneous adverse reactions."

Exposure-adjusted incidence rates (EAIRs) were calculated (as events per 100 subject treatment years) for AEs with onset during periods when the simultaneous criteria were not met (Table 1), and periods before and during when SC were met (Table 2).[21] Incidence rate ratios were calculated to compare AEs with onset during time periods based on whether SC were met or not. The start date when the SC were met for the first time corresponds to the first date when both criteria (i.e., serum ferritin < 1000 mcg/L and deferasirox dose >25 mg/kg/day) occurred simultaneously. The end date of the "during criteria met" period corresponds to the first date when one of the two criteria is not met anymore.

Table 1: Categorical analysis of adverse events for patients who never met Simultaneous Criteria by period (from IR response 20Dec2017) – SC not met (N = 1093)

	SC not met (N=1093)	
	N. of events	EAIR per 100 STY
Overall AEs	878	124.5
SOC – hepatobiliary disorders	51	2.3
SOC – renal and urinary disorders	55	2.4
Overall SAEs	137	6.4
SAEs from SOC – hepatobiliary disorders	12	0.5
SAEs from SOC - renal and urinary disorders	10	0.4
AESIs	347	18.6

SC = Simultaneous criteria (Exjade dose >25mg/kg/day and serum ferritin <1000 µg/L)
EAIR = Exposure Adjusted Incidence Rate
STY = Subject Treatment Years
AESIs = Adverse Events of Special Interest (as defined by the sponsor)

[20] Novartis 22-Aug-2017 response (NDA 21882, Seq #0224, includes datasets) to the FDA information requests dated 7-Jul-2017 and 20-Jul-2017

[21] Novartis 21-Dec-2017 (NDA 21882, Seq #0234) response to the FDA information request dated 11-Dec-2017

Table 2: Categorical analysis of adverse events for patients who met SC by period (from IR response 20Dec2017) – SC met (N = 158) – periods before and during (first episode)

	SC met (N=158)			
	Before criteria met		During criteria met	
	N. of events	EAIR per 100 STY	N. of events	EAIR per 100 STY
Overall AEs	128	137.8	71	180.9
SOC – hepatobiliary disorders	6	1.8	2	2.9
SOC – renal and urinary disorders	5	1.5	6	9
Overall SAEs	23	7.4	7	10.3
SAEs from SOC – hepatobiliary disorders	0	0	1	1.5
SAEs from SOC - renal and urinary disorders	0	0	2	2.9
AESIs	37	13.1	15	25
Dose interruption ≥1	54	23.3	33	47.9

SC = simultaneous criteria (Exjade dose >25mg/kg/day and serum ferritin <1000 µg/L)
EAIR = Exposure Adjusted Incidence Rate
STY = Subject Treatment Years
AESIs = Adverse Events of Special Interest (as defined by the sponsor)

As shown in Table 3 below, the exposure-adjusted incidence rate for adverse events overall (p = 0.002), and renal and urinary disorders (p = 0.001), was higher during periods when patients received Exjade dose >25 mg/kg/day concurrently with serum ferritin values <1000 mcg/L, compared to patients who did not receive dose >25 mg/kg/day when serum ferritin was <1000 mcg/L (i.e. reference = 1093 patients who did not meet the simultaneous criteria during the study).

Table 3: Categorical analysis of adverse events for patients who met Simultaneous Criteria (SC) by period (SC met versus SC never met)

	During SC met vs SC not met		
	IRR	95% CI	P-value (2 sided)
Overall AEs	1.453	1.141, 1.85	0.002
SOC – hepatobiliary disorders	1.261	0.2063, 4.348	0.69
SOC – renal and urinary disorders	3.750	1.615, 8.709	0.001
Overall SAEs	1.609	0.7531, 3.439	0.21
SAEs from SOC – hepatobiliary disorders	3.000	0.139, 17.32	0.35
SAEs from SOC - renal and urinary disorders	7.250	1.081, 29.72	0.04
AESIs	1.344	0.8016, 2.254	0.26

Note: Mid-P exact test, P-value and 95%CI were applied when N. of events <=5.
AESIs = Adverse Events of Special Interest (as defined by the sponsor)

For these same 158 pediatric patients in the pooled clinical trial analysis who received Exjade dose >25 mg/kg/day when serum ferritin was <1000 µg/L, the exposure-adjusted incidence rate of renal and urinary disorder adverse events was 6-fold higher (p 0.005), and deferasirox dose was interrupted 2-fold more often (p 0.001), during periods when patients received Exjade dose >25 mg/kg/day concurrently with serum ferritin <1000 µg/L, compared to study time before those conditions were met, as shown below in Table 4.

Table 4: Categorical analysis of adverse events for patients who met Simultaneous Criteria (SC) by period (during SC first met versus before SC met)

	During SC met vs Before SC met		
	IRR	95% CI	P-value (2 sided)
Overall AEs	1.313	0.9823, 1.754	0.065
SOC – hepatobiliary disorders	1.611	0.2238, 7.612	0.55
SOC – renal and urinary disorders	6.000	1.75, 21.36	0.005
Overall SAEs	1.392	0.5973, 3.244	0.44
SAEs from SOC – hepatobiliary disorders	–	–	–
SAEs from SOC - renal and urinary disorders	–	–	–
AESIs	1.908	1.047, 3.477	0.03
Dose interruption ≥1	2.056	1.333, 3.17	0.0008

Note: Mid-P exact test, P-value and 95%CI were applied when N. of events <=5.
AESIs = Adverse Events of Special Interest (as defined by the sponsor)

5 STUDY CICL670A2411 - 5-YEAR PEDIATRIC REGISTRY

A 5-year pediatric registry (Study CICL670A2411, titled, "A 5 Year Observational Study (Registry) of Children Aged 2 To <6 Years at Enrollment with Transfusional Hemosiderosis Treated with Deferasirox") was conducted by the sponsor in fulfillment of Subpart H Postmarketing Study Commitment (PMC) 750-1 which was issued at the time of approval to obtain additional safety information on deferasirox in young pediatric patients. The Final Study Report was submitted by the sponsor on January 29, 2016 and has been reviewed by DHP.

Serum creatinine was measured monthly for most children participating in the registry; however, many study sites evaluated serum creatinine results using reference ranges that may not have been age-appropriate. Since the oldest children in Study 2411 would have been less than 12 years old while participating in the registry, the upper limit of normal (ULN) for serum creatinine would not have been expected to exceed 62 µmol/L (0.7 mg/dL) based on standard published reference ranges. However, our analysis of the dataset found that 44 of the 53 study centers (83%) had ULN values >62 µmol/L.[22] Variability in the serum creatinine ULN used among the study sites, and the likelihood that many ULN cut-points were not age-appropriate for young children, hinders interpretation of the sponsor's stated results regarding the number of children who developed serum creatinine values >ULN during the study. For this reason, an analysis of the clinical laboratory dataset from Study 2411 was conducted by DEPI to assess patterns of kidney injury measured as decreases in eGFR. The sponsor was asked to provide a dataset with eGFR values calculated using the appropriate Schwartz equation depending on which assay method was used for measure serum creatinine. [23]

[22] Ceriotti F, Boyd JC, Klein G, Henny J, Queraltó J, Kairisto V, Panteghini M; IFCC Committee on Reference Intervals and Decision Limits (C-RIDL). Reference intervals for serum creatinine concentrations: assessment of available data for global application. Clin Chem. 2008 Mar;54(3):559-66.

[23] Novartis 2-Feb-2018 (NDA 21882, Seq #0235) response to the FDA information request dated 19-Jan-2018

Of the 267 pediatric patients enrolled in the 5-year Registry, 242 patients had pre- and post-baseline eGFR measurements. Of these, 116 (48%) patients had a decrease in eGFR of ≥33% observed at least once. Twenty-one (18%) of these 116 patients with decreased eGFR had a dose interruption, and 15 (13%) of these 116 patients had a dose decrease within 30 days.

6 CONCLUSION

Clinically important AKI that could result in increased deferasirox levels, and potential exposure-related nephrotoxicity, occurred commonly in young children participating in a 5-year Registry (Study 2411), and often was followed by a dose decrease or interruption of therapy. This scenario suggests that the published case reports and FAERS data describing severe toxicity and multi-organ failure could be preceded by AKI due to overchelation when deferasirox dose is disproportionately high compared to the body iron burden. Results of a nested case-control study of pooled clinical trial data in pediatric transfusion-dependent thalassemia patients receiving deferasirox confirm that risk of AKI is markedly elevated when the dose of deferasirox is high compared to the body iron burden, as represented by serum ferritin levels. A similar clinical pattern was observed in an analysis of clinical adverse events in the pooled clinical trial dataset, and was notable for an increased risk of renal adverse events, adverse events of special interest (as defined by the sponsor), and the occurrence of adverse events which necessitated therapy interruptions.

These results highlight the importance of clinical laboratory monitoring to identify relatively lower levels of body iron burden in children taking deferasirox. Risk of severe toxicity associated with overchelation may be mitigated by using the lowest possible dose to establish and maintain an acceptable level of body iron burden. Deferasirox therapy should be interrupted or discontinued in children with evidence of AKI, and during acute illnesses, or other conditions which may predispose to volume depletion.

7 RECOMMENDATIONS

We recommend the addition of the following language to Section 6 ADVERSE REACTIONS of the product labeling for Exjade, and similar language for Jadenu, reflecting the equivalent dosage for the different formulations of deferasirox:

7.1 POOLED ANALYSIS OF PEDIATRIC CLINICAL TRIAL DATA

A nested case control analysis was conducted within a deferasirox pediatric pooled clinical trial dataset to evaluate the effects of dose and serum ferritin level, separately and combined, on kidney function. Among 1213 children (aged 2 to 15 years) with transfusion-dependent thalassemia, 162 cases of acute kidney injury (eGFR ≤90 ml/min/1.73m^2) and 621 matched-controls with normal kidney function (eGFR ≥120 ml/min/1.73m^2) were identified. The primary findings were:

- A 26% increased risk of acute kidney injury was observed with each 5 mg/kg increase in daily deferasirox dosage starting at 20 mg/kg/day (95% CI: 1.08-1.48)
- A 25% increased risk for acute kidney injury was observed with each 250 mcg/L decrease in serum ferritin starting at 1250 mcg/L (95% CI: 1.01-1.56).
- Among pediatric patients with a serum ferritin <1000 µg/L, those who received deferasirox dosage >30 mg/kg/day, compared to those who received lower dosages,

had a 4.5-fold higher risk for acute kidney injury (95% CI: 1.25-15.95), consistent with overchelation.

In addition, a cohort based analysis of adverse events was conducted in the deferasirox pediatric pooled clinical trial data. Pediatric patients who received deferasirox dose >25 mg/kg/day when their serum ferritin was <1000 mcg/L (n=158) had a 6-fold greater rate of renal adverse events (95% CI: 1.75-21.36) and a 2-fold greater rate of dose interruptions (95% CI: 1.33-3.17) compared to the time-period prior to meeting these simultaneous criteria. Adverse events of special interest (renal, hearing disorders, cytopenia, and gastrointestinal) occurred 1.9-fold more frequently when these simultaneous criteria were met, compared to preceding time-periods (95% CI: 1.05-3.48).

7.2 5-YEAR PEDIATRIC REGISTRY

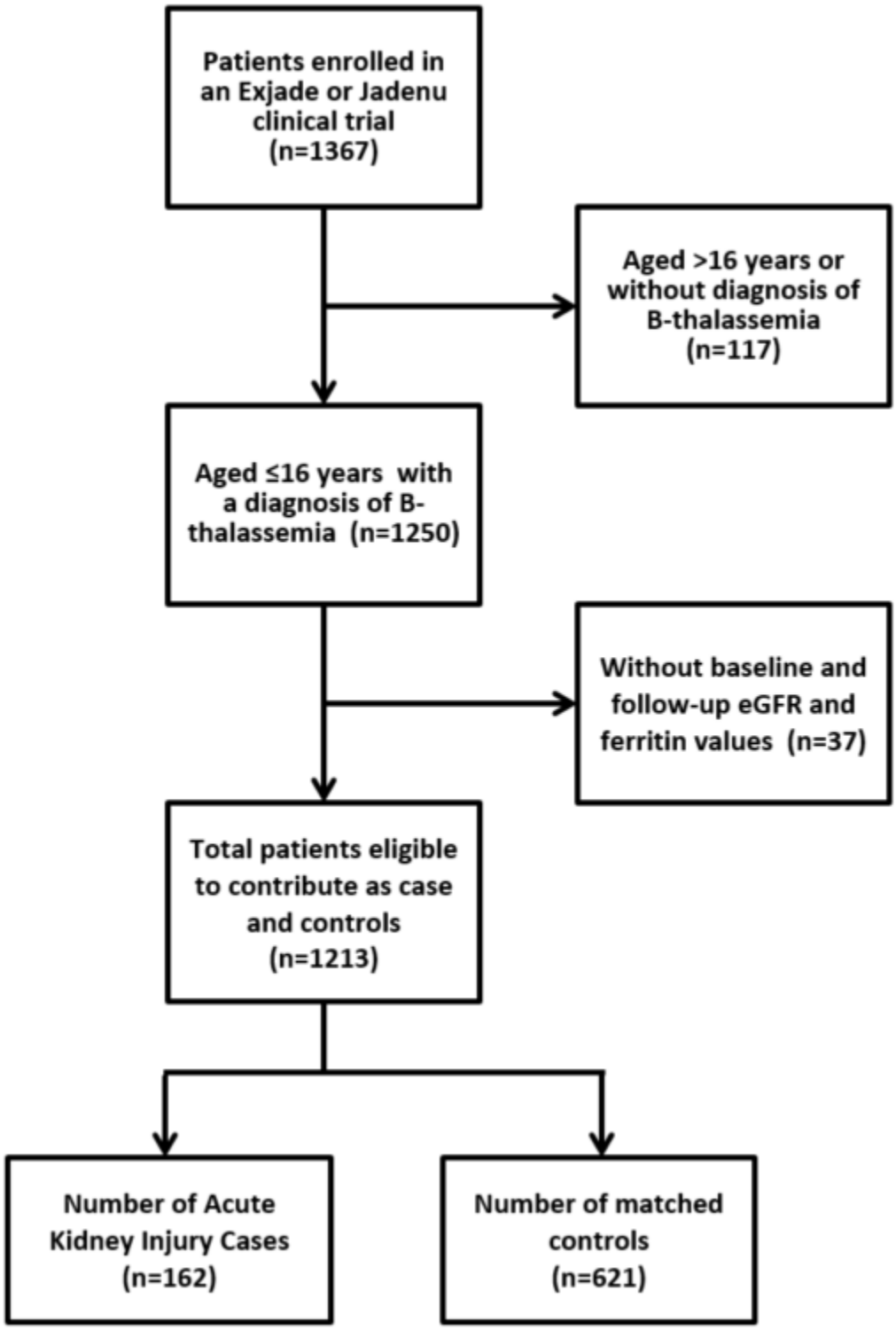
In a 5-year observational study, 267 pediatric patients 2 to <6 years of age (at enrollment) with transfusional hemosiderosis received deferasirox. Of the 242 patients who had pre- and post-baseline eGFR measurements, 116 (48%) patients had a decrease in eGFR of $\geq$33% observed at least once. Twenty-one (18%) of these 116 patients with decreased eGFR had a dose interruption, and 15 (13%) of these 116 patients had a dose decrease within 30 days. Adverse events leading to permanent discontinuation from the study included liver injury (n=11), renal tubular dysfunction (n=3), vomiting (n=2), abdominal pain (n=1), and hypokalemia (n=1).

8 APPENDICES

8.1 APPENDIX 1: DESCRIPTION OF CLINICAL TRIALS INCLUDED IN THE POOLED DATASET

Study	Study Title	Study Timeframe	Study Type
CICL670A0106	An open label, phase 11a study to evaluate the safety, tolerability, pharmacokinetics and the effects on liver iron concentration of repeated doses of 10 mg/kg/day of ICL670 administered to pediatric patients with transfusion dependent β thalassemia, followed by an extension study	9/3/02 – 6/3/04	Interventional
CICL670A0107	A randomized, comparative, open label phase III trial on efficacy and safety of long-term treatment with ICL670 (5 to 40 mg/kg/day) in comparison with deferoxamine (20 to 60 mg/kg/day) in β-thalassemia patients with transfusional hemosiderosis, followed by an extension study	6/13/00 – 11/2/04	Interventional
CICL670A2206	A multi-center, randomized, open-label Phase II trial evaluating deferasirox compared with deferoxamine in patients with cardiac iron overload due to chronic blood transfusions (CORDELIA) including a one-year extension	11/26/07 – 3/5/13	Interventional
CICL670A2301	A non-interventional study to evaluate the long-term safety of deferasirox treatment in adult and pediatric patients ≥ 2 years old with chronic transfusional iron overload in actual practice setting. (SENTINELLE)	7/04/11 – 10/30/15	Observational
CICL670A2402	An open-label, multi-center trial on efficacy and safety of long-term treatment with ICL670 (10 to 20 mg/kg/day) in β thalassemia patients with transfusional hemosiderosis	5/27/04 – 11/24/06	Interventional
CICL670A2409	A one-year, open-label, single arm, multi-center trial evaluating the efficacy and safety of oral ICL670 (20 mg/kg/day) in patients diagnosed with transfusion-dependent iron overload	4/19/05 – 7/15/09	Interventional
CICL670A2411	A 5-year observational study (registry) of children aged 2 to less than 6 years at enrollment with transfusional hemosiderosis treated with deferasirox (ENTRUST)	1/17/07 – 6/12/15	Observational
CICL670F2201	A randomized, open-label, multicenter, two arm, phase II study to investigate the benefits of an improved deferasirox formulation (FCT) (ECLIPSE)	7/8/14 – 2-24-16	Interventional
CICL670A0108	A multi-center, open-label, non-comparative, phase II trial on efficacy and safety of ICL670 (5-40 mg/kg/day) given for at least 1 year to patients with chronic anemias and transfusional hemosiderosis unable to be treated with deferoxamine, followed by an extension study	1/6/03 – 11-17-04	Interventional
CICL670A2214	A Phase II, open-label, single-arm, multicenter study to evaluate the efficacy and safety of deferasirox in combination with deferoxamine followed by deferasirox monotherapy in patients with severe cardiac iron overload due to chronic blood transfusion (HYPERION)	1/19/11 – 11/18/13	Interventional

8.2 APPENDIX 2: IDENTIFICATION OF AKI CASES AND MATCHED CONTROLS



8.3 APPENDIX 3: CHARACTERISTICS OF AKI CASES AND MATCHED CONTROL VISITS

Patient Characteristics	Acute Kidney Injury *n=162*	Control Visit *n=621*	Chi-Squared (T-test)
Study			0.66
CICL670A0106	3 (1.9%)	6 (1.0%)	
CICL670A0107	55 (34.0%)	210 (33.8%)	
CICL670A2206	1 (0.6%)	1 (0.2%)	
CICL670A2301	2 (1.2%)	2 (0.3%)	
CICL670A2402	23 (14.2%)	90 (14.5%)	
CICL670A2409	42 (25.9%)	168 (27.1%)	
CICL670A2411	36 (22.2%)	144 (23.2%)	
Gender			0.90
Female	81 (50.0%)	314 (50.6%)	
Male	81 (50.0%)	307 (49.4%)	
Baseline Age			0.94
2 to 6 years	67 (41.4%)	255 (41.1%)	
7 to 15 years	95 (58.6%)	366 (58.9%)	
Mean (SD), *years*	8 (4)	8 (4)	(0.88)
Median (range)*, years*	8 (2-15)	8 (2-15)	
Duration of Exposure			
Mean (SD)	465 (408)	458 (394)	(0.83)
Median (range)	311 (15-1761)	315 (21-1771)	

8.4 APPENDIX 4: RISK FOR AKI BY DEFERASIROX DOSE AND SERUM FERRITIN LEVEL, USING THREE CASE DEFINITIONS

	Cases n (%)	Controls n (%)	Rate Ratio (95%CI)	P-value
Primary Analysis: AKI defined as eGFR ≤90 ml/min/1.73m²				
	n = 162	*n = 621*		
Dose[1]				
5mg/kg/day increments	--	--	1.26 (1.08, 1.48)	<0.01
>25 mg/kg/day	85 (52.5)	284 (45.7)	1.40 (0.94, 2.09)	0.10
>30 mg/kg/day	53 (32.7)	149 (24.0)	1.73 (1.13, 2.63)	0.01
Ferritin[2]				
250µg/L decrease (from 1250µg/L)	--	--	1.25 (1.01, 1.56)	0.04
<750 mcg/L	11 (6.8)	24 (3.9)	2.01 (0.96, 4.23)	0.06
<1000 mcg/L	23 (14.2)	61 (9.8)	1.85 (1.08, 3.17)	0.02
<1250 mcg/L	42 (25.9)	156 (25.1)	1.40 (0.87, 2.24)	0.17
Secondary Analysis: AKI defined as eGFR ≤100 ml/min/1.73m²				
	n = 287	*n = 1109*		
Dose[1]				
5mg/kg/day increments	--	--	1.20 (1.06, 1.34)	<0.01
>25 mg/kg/day	139 (48.4)	456 (41.1)	1.42 (1.05, 1.91)	0.02
>30 mg/kg/day	85 (29.6)	249 (22.5)	1.54 (1.11, 2.13)	0.01
Ferritin[2]				
250µg/L decrease (from 1250µg/L)	--	--	1.03 (0.87, 1.24)	0.71
<750 mcg/L	16 (5.6)	52 (4.7)	1.41 (0.78, 2.56)	0.26
<1000 mcg/L	32 (11.1)	115 (10.4)		0.34
<1250 mcg/L	38 (13.2)	182 (16.4)	0.86 (0.58, 1.29)	0.47
Secondary Analysis: AKI defined as eGFR ≤80 ml/min/1.73m²				
	n = 86	*n = 325*		
Dose[1]				
5mg/kg/day increments[1]	--	--	1.36 (1.09, 1.69)	<0.01
>25 mg/kg/day	49 (57.0)	156 (48.0)	1.52 (0.88, 2.63)	0.14
>30 mg/kg/day	33 (38.4%)	84 (%)	2.01 (1.14, 3.54)	0.02
Ferritin[2]				
250µg/L decrease (from 1250µg/L)	--	--	1.19 (0.93, 1.53)	0.17
<750 mcg/L	11 (12.8)	28 (%)	1.99 (0.90, 4.38)	0.09
<1000 mcg/L	17 (19.8%)	55 (%)	1.72 (0.90, 3.27)	0.10
<1250 mcg/L	21 (24.4%)	87 (%)	1.14 (0.64, 2.05)	0.66

[1] Models adjusting for serum ferritin level in 250mcg/L decrements, starting at 1250mcg/L

[2] Models adjusting for deferasirox dose, defined in 5mg/kg/day increments starting at 20mg/kg/day

eGFR = estimated glomerular filtration rate

8.5 APPENDIX 5: THE EFFECT OF DEFERASIROX DOSE AND SERUM FERRITIN, SEPARATELY AND COMBINED, ON RISK FOR AKI

	Cases n (%)	**Controls** n (%)	**Rate Ratio** (95%CI)	**P-value**
	n = 162	*n = 621*		
Dose Effect[1]				
5mg/kg/day increments	--	--	1.26 (1.08, 1.48)	<0.01
>25 mg/kg/day	85 (52.5)	284 (45.7)	1.40 (0.94, 2.09)	0.10
>30 mg/kg/day	53 (32.7)	149 (24.0)	1.73 (1.13, 2.63)	0.01
Ferritin Effect[2]				
250µg/L decrease (from 1250µg/L)	--	--	1.25 (1.01, 1.56)	0.04
<750 mcg/L	11 (6.8)	24 (3.9)	2.01 (0.96, 4.23)	0.06
<1000 mcg/L	23 (14.2)	61 (9.8)	1.85 (1.08, 3.17)	0.02
<1250 mcg/L	42 (25.9)	156 (25.1)	1.40 (0.87, 2.24)	0.17
Combined Dose and Ferritin Effect[3]				
Low Ferritin when Dose is High	7 of 53 (13.2)	6 of 149 (4.0)	4.08 (1.26-13.21)	0.02
Low Ferritin when Dose is Low	16 of 109 (14.7)	55 of 472 (11.7)	1.52 (0.82-2.84)	0.19
High Dose when Ferritin is Low	7 of 23 (30.4)	6 of 61 (9.8)	4.47 (1.25-15.95)	0.02
High Dose when Ferritin is High	46 of 139 (33.1)	143 560 (25.5)	1.67 (1.07-2.61)	0.02

[1] Models adjusting for serum ferritin level in 250mcg/L decrements, starting at 1250mcg/L

[2] Models adjusting for deferasirox dose, defined in 5mg/kg/day increments starting at 20mg/kg/day

[3] Models adjusting for deferasirox dose >30mg/kg/day (i.e. high dose), serum ferritin <1000mcg/L (i.e. low ferritin), and their interaction

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