Deferasirox (Exjade® / Jadenu®)

Pediatric Focused Safety Review

An analysis of pediatric clinical data from pooled clinical studies

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Analysis of pediatric data in pooled clinical studies

- Through an information request to Novartis, clinical study datasets for deferasirox-treated pediatric patients were obtained by FDA
- The pooled clinical study datasets included company-sponsored interventional and prospective observational clinical studies.
- Ten deferasirox clinical studies were identified which included pediatric patients with prospective collection of clinical laboratory data.
- All data presented are for Exjade because the pooled dataset contained few patients receiving Jadenu for transfusion dependent thalassemia.

Analysis of pediatric data in pooled clinical studies - Study Objectives

- To investigate whether relatively higher deferasirox dose and relatively lower body iron burden (measured by serum ferritin level), together or independently, increase the risk for acute kidney injury (AKI)
- To determine whether the exposure-adjusted incidence rates of clinical adverse events are increased when Exjade dose is >25 mg/kg/day and serum ferritin is <1000 mcg/L

Analysis of clinical laboratory data using a nested case control study design to compare cases of acute kidney injury (AKI) with normal controls

POOLED ANALYSIS OF PEDIATRIC CLINICAL STUDY DATA – CLINICAL LABORATORY DATA

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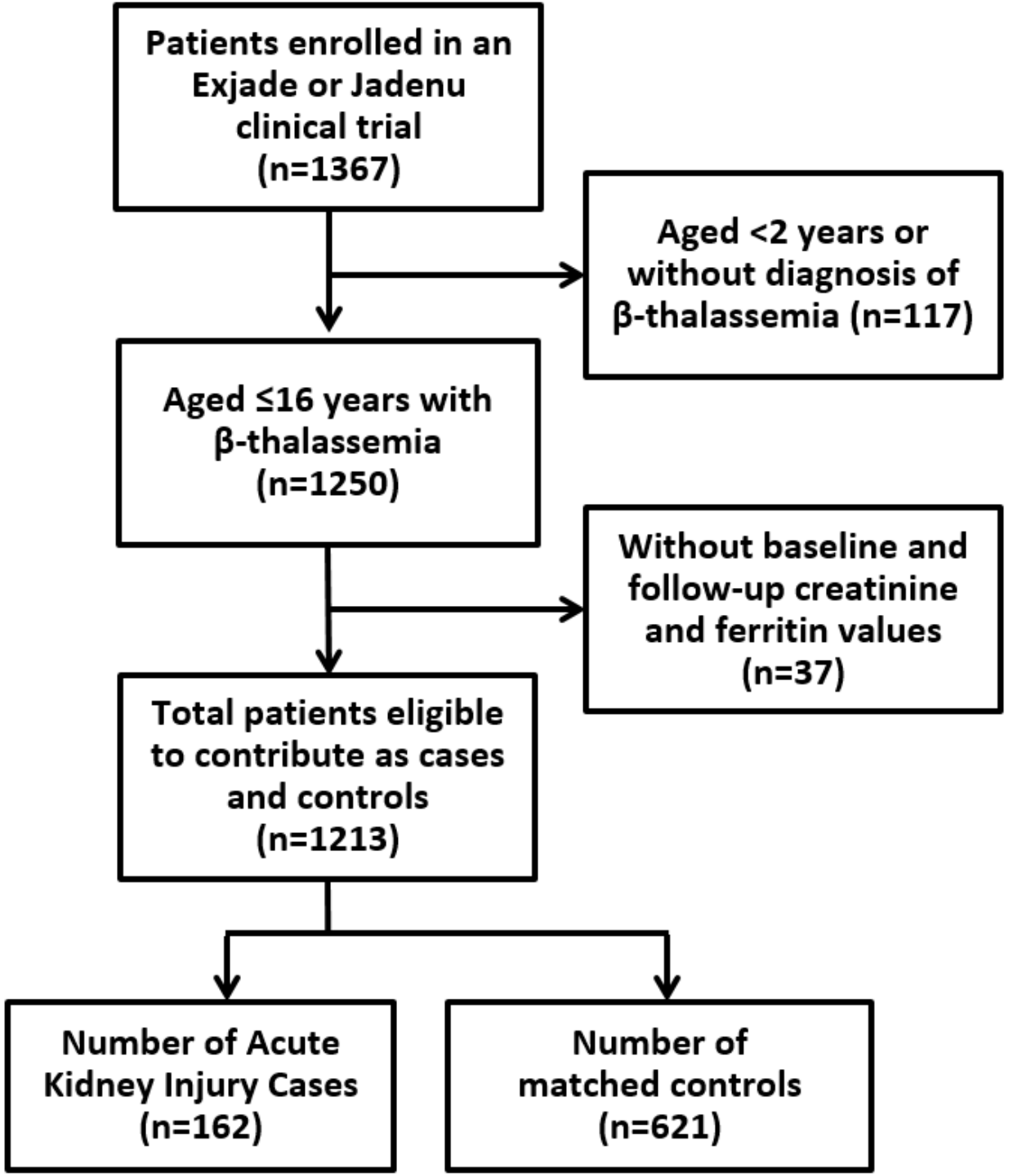

Patients enrolled in an Exjade or Jadenu clinical trial (n=1367)
Aged <2 years or without diagnosis of β-thalassemia (n=117)
Aged ≤16 years with β-thalassemia (n=1250)
Without baseline and follow-up creatinine and ferritin values (n=37)
Total patients eligible to contribute as cases and controls (n=1213)
Number of Acute Kidney Injury Cases (n=162)
Number of matched controls (n=621)

High-Level Study Design Elements

- Renal function was assessed monthly in most patients, using the estimated Glomerular Filtration Rate (eGFR)
- Acute Kidney injury (AKI) cases were defined as an eGFR ≤90 mL/min/1.73m^2
- Controls defined as an eGFR ≥120 mL/min/1.73m^2
- Dosage in mg/kg/day and serum ferritin in mcg/L were available throughout follow-up.
- Conditional Logistic Regression was used to assess the association between high-dose deferasirox and/or low serum ferritin and the outcome of acute kidney injury.

Effect of Exjade dose on risk for AKI

	Rate Ratio (95% CI)	P-value
Exjade Dose		
5mg/kg/day increments	1.26 (1.08-1.48)	0.004
Elevated-dose: >25 mg/kg/day	1.40 (0.94-2.09)	0.10
High-dose: >30 mg/kg/day	1.73 (1.13-2.63)	0.01

- A 26% increased AKI risk was observed per 5mg/kg/day increase in Exjade dosage above the typical starting dose of 20mg/kg/day

- Larger AKI risk was observed above larger dose thresholds, with a 73% increased AKI risk above Exjade dose 30mg/kg/day

Effect of serum ferritin level on risk for AKI

	Rate Ratio (95% CI)	P-value
Serum Ferritin		
250mcg/L decrease (from 1250mcg/L)	1.25 (1.01-1.56)	0.04
<750 mcg/L	2.01 (0.96-4.23)	0.06
<1000 mcg/L	1.85 (1.08-3.17)	0.02
<1250 mcg/L	1.40 (0.87-2.24)	0.17

- A 25% increased AKI risk was observed per 250mcg/L decrease in serum ferritin starting from 1250mcg/L.

- Larger AKI risk was observed below decreasing serum ferritin thresholds, with an 85% increased AKI risk below levels <1000mcg/L

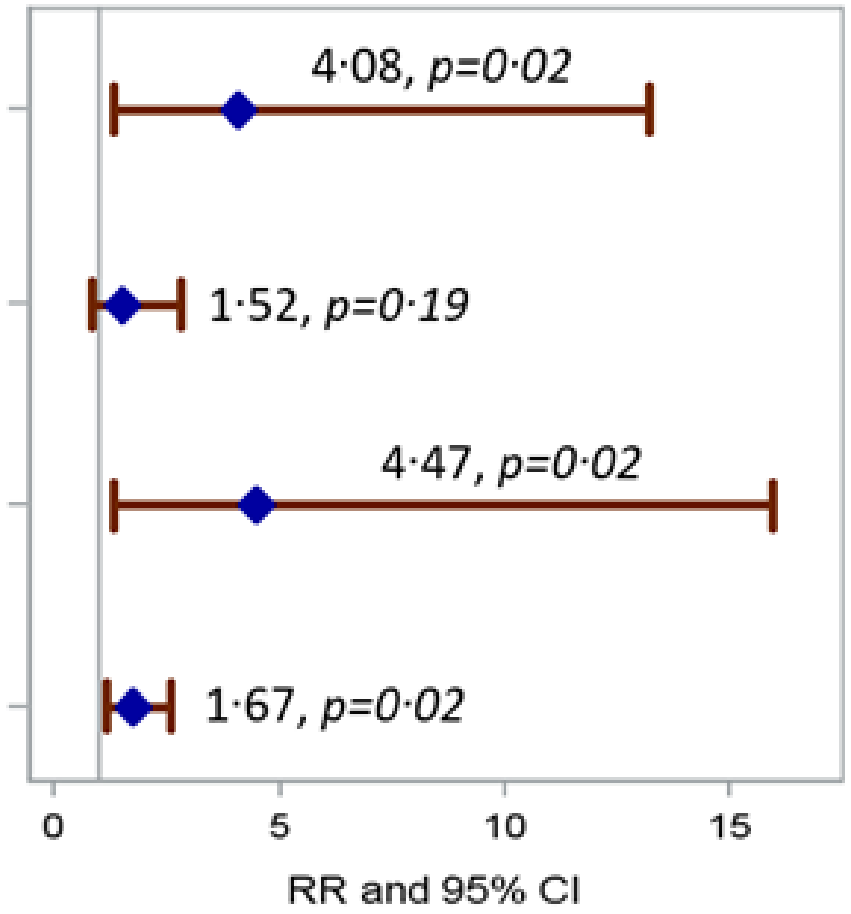
Combined effects of serum ferritin < 1000mcg/L and Exjade dosage >30mg/kg/day on risk for AKI

Effect of low serum ferritin
When deferasirox dose is high

Effect of low serum ferritin
when deferasirox dose is ***not*** high

Effect of high deferasirox dose
When serum ferritin is low

Effect of high deferasirox dose
When serum ferritin is ***not*** low



Effect of age on AKI risk

	Age 2-6 years *Rate Ratio (95% CI)*	Age 7-15 years *Rate Ratio (95% CI)*
Exjade Dose		
5mg/kg/day increments	1.41 (1.09-1.84)	1.19 (0.97-1.46)
High-dose: >30 mg/kg/day	2.21 (1.10-4.43)	1.43 (0.83-2.48)
Serum Ferritin		
250µg/L decrease (from 1250µg/L)	1.38 (1.01-1.87)	1.18 (0.86-1.63)
<1000 mcg/L	2.35 (1.10-5.01)	1.52 (0.69-3.36)

- Numerically larger risk was observed in younger pediatric patients
- Differential risk by age did not achieve statistical significance

AKI Case Summary and Disposition

- AKI cases had a mean 50.2% eGFR decrease from baseline, compared with a 6.9% eGFR decrease in controls.
- Most AKI cases (95.7%) had a documented recovery to eGFR >100 ml/min/1.73m^2.
- After the initial AKI episode, deferasirox treatment was discontinued in eleven patients and the dose was decreased in twelve patients.
- Among patients who recovered, 62 patients had a subsequent episode of AKI, of whom 30 patients had a third episode, and 16 patients had 4 or more episodes of AKI during the study.

Analysis of exposure-adjusted incidence rates of adverse events comparing time periods when Exjade dose was >25 mg/kg/day and serum ferritin was <1000 mcg/L, with preceding study periods

POOLED ANALYSIS OF PEDIATRIC CLINICAL STUDY DATA – ADVERSE EVENT ANALYSIS

Kate Gelperin, MD, MPH, OSE/DEPI-1

Analysis of clinical adverse events before and during simultaneous criteria

- Adverse events (AEs) were identified with onset during the first period with Exjade dose >25 mg/kg/day and serum ferritin <1000 mcg/L
  - Referred to as meeting "simultaneous criteria (SC)"
- Exposure adjusted incidence rates (EAIR) were calculated as the number of AE per 100 subject treatment years for:
  - 1) The first time period where simultaneous criteria were met
  - 2) Time period before meeting simultaneous criteria
    - Incidence rate ratios were calculated.

Clinical Adverse Events

	Exposure Adjusted Incidence Rates		RR (95%CI)
	Before SC Met [1]	*SC Met* [1]	
Overall Adverse Events (AE)	137.8	180.9	1.31 (0.98-1.75)
Hepatobiliary Disorders[2]	1.8	2.9	1.61 (0.22-7.61)
Renal and Urinary Disorders[2]	1.5	9	6.0 (1.75-21.4)
Overall Serious Adverse Events[3]	7.4	10.3	1.29 (0.60-3.2)
Hepatobiliary Disorders[2]	--	1.5	--
Renal and Urinary Disorders[2]	--	2.9	--
Adverse Events of Special Interest[4]	13.1	25	1.91 (1.05-3.48)
Dose interruption (≥1)	23.3	47.9	2.06 (1.33-3.17)

[1] SC = Simultaneous criteria = Exjade dose >25mg/kg/day and serum ferritin <1000 mcg/L

[2] Classified using System Organ Class from MedDRA dictionary

[3] Serious AE: requiring hospitalization, prolonged hospitalization, life-threatening, or fatal

[4] gastrointestinal hemorrhage, ulcer, esophagitis, hearing loss, increased liver transaminases, lens opacities, retinal changes, optic neuritis, peripheral blood cytopenias, renal disorders, and severe cutaneous reactions

A 5 Year Observational Study (Registry) of Children Aged 2 To <6 Years at Enrollment with Transfusional Hemosiderosis Treated with Deferasirox

STUDY CICL670A2411

5-YEAR PEDIATRIC REGISTRY

5-year Pediatric Registry

- Serum creatinine was measured monthly for most children; however, many study sites evaluated serum creatinine (CREA) results using reference ranges that may not have been age-appropriate
  - CREA ULN values were >62 µmol/L for 44 of 53 study centers [83%]
  - For children less than 12 years old, the CREA ULN reference range should be less than 62 µmol/L (0.7 mg/dL)
- Variability in the ULN used among the study sites, and the likelihood that many ULN cut-points were not age-appropriate, hinders interpretation of the sponsor's stated results regarding the number of children who developed serum creatinine values >ULN during the study
- FDA conducted an analysis of the clinical laboratory data from Study 2411 to evaluate changes in eGFR and AKI

5-year Pediatric Registry

- Of the 267 pediatric patients enrolled in Study 2411, 242 children had pre- and post-baseline eGFR measurements available for analysis
- Of these, 116 (48%) children had a decrease in eGFR of ≥33% observed at least once during the study
  - Of these, 21 children (18% of 116) had a dose interruption within 30 days of the eGFR decrease, and
  - An additional 15 children (13% of 116) had a dose decrease within 30 days of the eGFR decrease.
- Clinical pharmacology studies with deferasirox show that decreases in eGFR can lead to increased deferasirox levels, and potential exposure-related toxicity.

Clinical Implications – Main Findings

- Results of the pooled analyses of clinical data support overchelation as a causative factor for AKI among pediatric patients
- Longitudinal analysis of eGFR values during 5-year pediatric registry shows that clinically important kidney injury occurs commonly
- To reduce potential for severe toxicity, consistent monitoring of kidney function (eGFR) and body iron burden (serum ferritin) with appropriate dose adjustments or interruption is critical
- Deferasirox therapy should be interrupted when impaired renal function is suspected or during acute illnesses with volume depletion

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