

Nisbet-Brown E, Olivieri N, Giardina P, Grady R, Neufeld E, Sechaud R, et al.  
**Effectiveness and Safety of ICL670 in Iron-loaded Patients with Thalassemia:**  
**A randomized, double-blind, placebo-controlled, dose-escalation trial.**  
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**Background:** Chronic iron overload results from repeated blood transfusions used to treat  $\beta$ -thalassemia, sickle cell disease, myelodysplastic syndrome, and other anemias. It can lead to multiple organ damage including diabetes, growth failure, hypogonadism, cardiac failure, and hepatotoxicity. Seventy percent of iron in the body is in erythrocytes and 30% is stored in other tissues as ferritin, primarily in the liver. The first line therapy for chronic iron overload is administration of an iron chelator that bind to iron to facilitates its excretion, which will decrease serum ferritin levels. Until recently, deferoxamine was the only FDA approved iron chelator available in the U.S. It is administered by subcutaneous infusions of 8-12 hours at least 5 days/week. Exjade® (deferisirox, ICL670) is the first orally active iron chelator FDA approved in the U.S. as a once daily dose for treatment of chronic iron overload.

**Study Objective:** To evaluate the short term efficacy, pharmacokinetic/pharmacodynamic properties, and safety of ICL670.

**Methodology:**

- **Trial Design:** Three armed cohort study
- **Subjects:** 24 male/female patients with  $\beta$ -thalassemia and transfusional iron overload
  - **Inclusion criteria:**
    - 16 years of age and older
    - Serum ferritin 1000-8000 mcg/L
    - Liver biopsy within 3 months showing  $\geq 3.5$  mg Fe/ g dry weight
    - At least 4 weeks of deferoxamine 20mg/kg/day
    - Post transfusion Hgb of  $\geq 130$  g/L
  - **Exclusion criteria:**
    - Patients who did not meet the inclusion criteria

**Procedures:** This cohort study was divided into three arms with at least 7 patients per arm. Two patients per arm were randomly assigned to placebo (n=6). Patients were treated with Exjade® (deferisirox, ICL670) or placebo for twelve consecutive days.

- 10mg/kg/day (n=5)
- 20mg/kg/day (n=6)
- 40mg/kg/day (n=7)

**Outcomes:**

- **Efficacy:** cumulative net iron excretion (NIE), unsaturated iron binding capacity (UIBC), and efficiency of chelation
- **Pharmacokinetics of ICL670 and the iron complex:** AUC 24hrs after the first dose, AUC at steady state, accumulation factor,  $C_{max}$ , and  $t_{1/2}$ .
- **Safety and tolerability:** incidence of adverse events, laboratory monitoring, physical exam

**Statistical Analysis:**

- Linear regression analysis

**Results:**

- **Efficacy:**
  - NIE was linearly related to the dose of ICL670 ( $r^2=0.54$ ,  $p<0.0001$ ) (Fig.5)
  - UIBC was dose related for the 10 and 40 mg/kg/day doses, but the 20mg/kg/day dose had similar results with the 10 mg/kg/day dose. (Fig.4)
  - Efficiency of chelation was 15.3% for 10mg/kg/day, 20.5% for 20mg/kg/day, and 15.6% for 40mg/kg/day.
- **Pharmacokinetics:**
  - AUC of ICL670 increased proportionally to the dose and after multiple doses. (Fig.3)
  - $C_{max}$  of ICL670 was achieved in ~2 hours after each dose, increased proportional to the dose, and increased after multiple doses
  - $t_{1/2}$  of ICL670 was 12-16 hours after multiple doses
  - Plasma levels of the iron complex did not correlate to the dose of ICL670
  - ICL670 and the iron complex are mainly excreted in the feces (84%)
- **Safety and Tolerability:**
  - Nine patients withdrew from the study due to adverse events, but only three were correlated with ICL670. All of the adverse events were a nonpruritic maculopapular rash that occurred at the 40mg/kg/day dose after 8-10 days of therapy. The rash resolved after discontinuation of the drug. (Table 2)
  - Four patients experienced transient elevations in liver transaminases which could be related to ICL670.
  - The most frequent adverse events were gastrointestinal: nausea, vomiting, diarrhea, and they occurred more frequently at the higher doses. (Table 3)
  - No clinically significant differences in laboratory values (i.e. zinc, copper, calcium, magnesium levels, BMP, or cholesterol)
  - No clinically significant differences in ECG, auditory, or ophthalmologic exams related to ICL670.

**Strengths**

- Informed consent
- Males and females
- Replaced patients lost in the study
- Study Design

**Weaknesses**

- Small sample size
- Limited patient population
- Baseline characteristics unequal
- Poor reporting of statistical analysis
- Cluttered graphs

**Author's Conclusions:** ICL670 appears to be well tolerated at doses 10-40mg/kg/day after short term therapy without serious adverse events. ICL670 at a dose of 20mg/kg/day is effective at inducing a net iron excretion, primarily from the feces. Once daily dosing of ICL670 will be effective in preventing iron overload in patients transfused with 12-15ml packed red blood cells/kg/month, but more long term studies are needed.

**Reviewer's Conclusions:** Deferasirox does appear to be well tolerated in this limited phase II study at doses of 10-20mg/kg/day. I agree with the author's conclusion that the 20mg/kg/day dosing will be effective at preventing iron accumulation in this population, since NIE values were similar to amounts of iron transfused in the average patient; however, this dosage does not appear to reduce iron storage to optimum levels needed to prevent cardiotoxicity (serum ferritin < 2500 mcg/L) in patients who are already iron overloaded. This study was probably not adequately powered to detect this difference in baseline and follow-up serum ferritin levels and more long term studies are needed to establish efficacy and safety.

### Other Pertinent Primary Literature

- Galanello R, Piga A, Alberti D, Rouan M, Bigler H, Sechaud R. **Safety, tolerability, and pharmacokinetics of ICL670, a new orally active iron-chelating agents in patients with transfusion-dependent iron overload due to  $\beta$ -thalassemia.** *J Clin Pharmacol* 2003; 43:565-572.
  - First study conducted in humans to determine a safe dose for clinical trials
  - Two period, randomized, double-blind, placebo-controlled parallel study
  - **Population:** 25 Caucasian Males age  $\geq 18$  yoa with  $\beta$ -Thalassemia and posttransfusional iron overload
  - **Dosing:** ICL670 was given at dosages of 2.5 to 80mg/kg as single doses
  - **Results:**
    - The most frequent adverse events reported were headache, nausea, and diarrhea. Nausea and diarrhea were seen in the 80mg/kg dose only. Other adverse events related to ICL670 were elevations in serum transaminases and serum creatinine.
    - Mean  $t_{max}$  1-3 hours, AUC and  $C_{max}$  increased proportional to dose, and mean  $t_{1/2}$  was 12-20 hours
    - Mean percentage of ICL670 chelated to iron was 15-31% without a dose relationship
  - **Author's conclusions:** This trial supports the further study of ICL670 in patients with iron overload and found no safety concerns.

### Unpublished Observations

- Cappellini M, Cohen A, Piga A, Bejaoui M, Perrotta S, Agaoglu L, et al. **A phase III study of deferasirox (ICL670), a once daily oral iron chelator, in patients with  $\beta$ -thalassemia.** Abstract. *Blood*. Prepublished Online. December 13, 2005.
  - Multicenter, open-label, randomized study comparing safety and efficacy of deferasirox and deferoxamine
  - **Population:** 552 patients  $\geq 2$  yoa with evidence of iron overload based on liver biopsy iron concentrations (LIC)
  - **Dosing:** Oral deferasirox 5, 10, 20, or 30 mg/kg/day versus deferoxamine SC infusions of 20-60mg/kg/day for at least 5 days/week, based on baseline LIC values, for 12 months
  - **Results:**
    - 52.9% of patients treated with deferasirox reached goal levels of LIC versus 66.4% of patients treated with deferoxamine. Mean change in LIC for deferasirox was -2.4mg Fe/g dry weight versus -2.9mg Fe/g dry weight for deferoxamine. Reductions in LIC with deferasirox were not reached until 20 and 30 mg/kg/day dosing.
    - The most frequent adverse events were abdominal pain, nausea, vomiting, and diarrhea, skin rashes, headache, pyrexia, cough, and increased serum creatinine.
  - **Author's Conclusions:** Deferasirox shows non-inferiority at doses of 20 and 30mg/kg/day and has potential for being an effective once-daily oral iron chelator in patients with transfusional iron overload.
- Porter J, Vichinsky E, Rose C, Piga A, Olivieri N, Gattermann N, et al. **A phase II study with ICL670 (deferasirox, Exjade®), a once-daily oral iron chelator, in patients with various transfusion-dependent anemias and iron overload.** *Blood* (ASH Annual Meeting Abstracts) 2004; 104: Abstract 3621.
  - Multicenter, open-label, non-comparative study of deferasirox in patients with various chronic anemias and transfusional iron overload to determine efficacy and safety
  - **Population:** 184 patients  $\geq 2$  yoa with evidence of iron overload based on liver biopsy iron concentrations (LIC) or SQUID imaging of the liver
  - **Dosing:** Oral deferasirox 5, 10, 20, or 30 mg/kg/day, based on baseline LIC values, for 12 months
  - **Results reported:** A mean reduction in LIC for deferasirox was 4.2mg Fe/g dry weight, which was statistically significant at dosages of 20 and 30 mg/kg/day ( $p < 0.001$ ).
  - **Author's conclusions:** Deferasirox is a safe and effective, once-daily oral iron chelator for treating chronic transfusional hemosiderosis.

**Clinical Application:** Deferasirox is a novel oral iron chelator that is only FDA approved for use in chronic iron overload due to blood transfusions. Deferoxamine, the only other available iron chelator, is approved for acute iron intoxication and chronic iron overload. Many of the key clinical trials evaluating deferasirox have not been published, preventing objective analysis of the efficacy of deferasirox compared to deferoxamine. While having an oral, once daily iron chelator will improve compliance and quality of life for patients with transfusional hemosiderosis, deferasirox has restricted availability through a distributor that provides the drug directly to the patient and will be unavailable from the neighborhood pharmacy.