

**2009 Annual Meeting of the
American Society of Hematology**

Highlights Report

**Two-Year Analysis of Efficacy and Safety of
Deferasirox (Exjade®) Treatment in Myelodysplastic
Syndrome Patients Enrolled in the US03 Study**

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Abstract 3829

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**Two-Year Analysis of Efficacy and Safety of Deferasirox (Exjade®) Treatment in Myelodysplastic Syndrome Patients Enrolled in the US03 Study
(Abstract # 3829)**

Alan F List, Maria R Baer, David Steensma, Azra Raza, Noelia Martinez-Lopez, Carole Paley, John Feigert and Emmanuel Besa

US03 is a phase II, ongoing, open-label 3-year trial (1 year core/2 year extension) of the iron chelator deferasirox in patients with Low- or Int-1 IPSS-risk MDS. It will provide data on the long-term safety and efficacy profile of deferasirox in transfused MDS patients who may require iron chelation therapy for many years.

173 patients enrolled with a mean serum ferritin level at baseline of 3313 ng/mL. All patients received a starting deferasirox dose of 20 mg/kg/day, and adjustments were permitted to 40 mg/kg/day based on tolerability and response. 95 patients completed the first year of treatment, 83 of whom participated in the 2-year extension phase. At baseline of the extension phase mean serum ferritin was 2496 ng/mL and mean deferasirox dose was 24.4 mg/kg/day (Table 1).

Table 1. Baseline characteristics of extension phase population (n=83)

Mean age (range), years	68 (21–90)
Female: male, n	42:41
IPSS risk group, n (%)	
Low	23 (28)
Int-1	60 (72)
Iron assessments and transfusions	
Mean serum ferritin, ng/mL	2496 (range: 546 – 7770)
Mean lifetime transfusions prior to study, n	83.6 (range: 20 – 365)
Mean years of transfusions prior to study, n (range)	4.6 (2-12)
Patients with MDS therapy at study entry, n (%)	
Darbepoetin, GCSF, Epo, tranexamic acid	18 (22)
Other MDS-specific therapies	13 (16)

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Calculated creatinine clearance at baseline, n (%)	
Normal (>80 mL/min)	20 (25%)
Abnormal: mild (51–80 mL/min)	41 (52%)
Abnormal: moderate (30–50 mL/min)	16 (20%)
Abnormal: severe (<30 mL/min)	2 (3%)

Despite an ongoing mean transfusion rate of 3.6 units/month, the mean serum ferritin level declined by 1088 ng/mL. Of the 50 patients who completed 24 months' treatment, the mean serum ferritin reduction was 951 ng/mL; 31/50 achieved a reduction in serum ferritin of at least 200 ng/mL. 6 patients' serum ferritin values were unchanged (+/- 200 ng/mL) and 13 had an increase of at least 200 ng/mL.

Of the 83 patients who entered the extension phase, 35 discontinued. Reasons for discontinuation were deaths (n=11), none of which were considered to be related to deferasirox, MDS progression/AML (n=8) and AEs (n=7). The most common adverse events were diarrhea, abdominal pain, nausea and increased serum creatinine.

Data from this extension study have confirmed the previously described efficacy and safety profile of deferasirox in patients with MDS. Despite ongoing transfusional iron intake, 31 of 50 patients had a decrease in serum ferritin of ≥ 200 ng/mL after 2 years. The rate of AEs in this elderly population is, as expected, higher than that in younger patients with thalassemia, and the dropout rate was approximately 40% per year. To determine whether decreases in serum ferritin correlate with clinical benefits, a large, prospective, randomized, control trial in low and INT-1 MDS patients is currently enrolling.

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Expert commentary: Dr John Porter, University College London, UK

The key questions are whether morbidity and/or mortality are improved in chelated patients as compared with placebo. It is not yet clear how rapidly after the onset of iron overload in MDS patients that significant complications of iron overload develop. By analogy with thalassemia major, reductions in serum ferritin are predicted to reduce iron-mediated morbidity in MDS. However this has not been 'proven' with prospective randomized trials.

One school of thought is that morbidity from transfusional iron overload will be similar irrespective of the underlying hematological condition and it is therefore unnecessary to show a benefit of chelation for each separate diagnosis.

Others believe it essential to show clinical benefit for each and every diagnostic patient group with transfusional iron overload. In my opinion this is unrealistic, as many forms of transfusional iron overload are too rare to conduct such studies, and it would be debatable ethically to design a study that withholds iron chelation in a group of patients who have hitherto been treated with chelators.

MDS is a large patient group and prospective trials are feasible. However, in my view trials should be designed so that patients who are potentially at risk from iron overload have the option to receive chelation at some point during the trial, if they take part in a study. A study comparing immediate versus delayed chelation therapy would address these issues as it would answer the question about the clinical efficacy of chelation therapy in MDS whilst offering all patients the prospect of therapy.