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Article type : Original Article

Deferasirox in children with transfusion-dependent thalassemia or sickle cell anemia: a large cohort real-life experience from Turkey (REACH-THEM)

Short title: Deferasirox in children with TDT and SCA

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ejh.13180
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ABSTRACT

Objectives: To evaluate the long-term efficacy and safety of deferasirox therapy in a large observational cohort of children with transfusion-dependent thalassemia (TDT) and sickle cell anemia (SCA) in Turkey.

Methods: This was a multicenter, prospective cohort study including TDT and SCA patients aged 2-18 years with iron overload (≥100 mL/kg of pRBC or a serum ferritin [SF] level >1000 µg/L) receiving deferasirox. Patients were followed for up to 3 years according to standard practice.

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Results: 439 patients were evaluated (415 [94.5%] TDT, 143 [32.6%] between 2-6 years). SF levels consistently and significantly decreased across 3 years of deferasirox therapy from a median of 1775.5 to 1250.5 µg/L ($p<0.001$). SF decreases were noted in TDT (1804.9 to 1241 µg/L), SCA (1655.5 to 1260 µg/L), and across age groups 2-6 years (1971.5 to 1499 µg/L), 7-12 years (1688.5 to 1159.8 µg/L), and 13-18 years (1496.5 to 1107 µg/L). SF decreases were also noted for all deferasirox dose groups but only significant in patients with doses ≥30 mg/kg/day (n=120, -579.6 median reduction, $p<0.001$). Only 9 (2%) patients had adverse events suspected to be related to deferasirox. Serum creatinine slightly increased but remained within the normal range.

Conclusions: Deferasirox has long-term efficacy and safety in children with TDT and SCA, although higher doses (≥30 mg/kg/day) may be required to achieve iron balance.

Keywords: iron overload, transfusion, iron chelation, pediatric, hemoglobinopathy.

INTRODUCTION

Iron overload remains a concern in regularly transfused patients with thalassemia and sickle cell anemia (SCA). In patients with transfusion-dependent thalassemia (TDT), iron accumulation in the body including vital organs like the liver, heart, and endocrine glands eventually leads to their dysfunction and subsequent morbidity and mortality (1). Iron accumulation starts at the outset of transfusion dependence in early childhood, and can quickly reach critical levels in the liver and heart before patients even grow into adulthood (2-5). Thus, prompt diagnosis and effective

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management of iron overload in childhood can ensure patients do not reach such critical iron toxicity levels and avoid often irreversible morbidity. The deleterious effects of iron overload in SCA have also been established, with observations of increased pain crisis, hospitalization rates, end-organ morbidity and mortality; although with notable absence of cardiac siderosis and associated morbidity (6-10). Iron overload can also affect growth and development in children with TDT and SCA further confirming the need for effective therapy of this secondary condition as early as possible (1, 11).

Data from randomized clinical trials have confirmed the efficacy and safety of the oral iron chelator, deferasirox, in both TDT and SCA, including patients as young as two years of age treated for up to five years (12, 13). However, outside the context of controlled clinical trials, several challenges may preclude effective management of patients in the real-life setting making it necessary to revisit the role of the chelator outside interventional trials. With this background, we aimed to evaluate the long-term efficacy and safety of deferasirox therapy in a large observational cohort comprised entirely of children with TDT and SCA receiving deferasirox for up to three years, to better characterize its role in children and to try to identify factors that may be addressed in future practice to ensure more effective therapy.

PATIENTS AND METHODS

This was a multicenter, nation-wide, non-interventional and observational, prospective cohort study performed across Turkey. The study cohort comprised consecutive patients presenting to the study centers (30 centers) over a one-year recruitment period, who were aged 2-18 years with a diagnosis of TDT or SCA and

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were receiving oral iron chelation therapy. To be eligible for enrollment, patients had to have iron overload defined as blood transfusion history of ≥100 mL/kg of packed red blood cells (approximately 10 units for a 20 kg patient) or a serum ferritin level consistently >1000 µg/L. Patients beginning or under treatment with deferasirox (under prescription) monotherapy at the time of enrollment for transfusional hemosiderosis or who switched to deferasirox from other chelators during the course of the study were included. The following patients were excluded: patients who had any contraindication for treatment with any iron chelator according to the local prescribing information, patients with non-transfusional hemosiderosis, patients unwilling or unable to comply with the study protocol, patients with severe concomitant illnesses that might make the completion of the study unlikely (e.g. cancer, active AIDS), patients involved in another clinical trial, pregnant or breastfeeding patients, patients with known sensitivity to class of oral iron chelator, and patients who used any investigational agent in the last 30 days.

Patients were followed for up to three years or until change of chelator, death, or loss to follow up. Follow-up visits and assessments were scheduled according to the standard practice of the center and treating physician's judgement and data, when available, were collected at baseline and every six months and included: demographics (age and gender), type and dose of iron chelation therapy, serum ferritin levels, as well as safety which was assessed by examining the occurrence of adverse events (AEs), and routine laboratory assessments including hemoglobin level, alanine aminotransferase (ALT) and serum creatinine (SCr). Laboratory testing was done locally at each participating institution. Deferasirox dosing for initiation,

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interruption, and adjustment followed local prescribing criteria and physician judgement.

The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The research was approved by local ethics committee of the coordinating site of participating sites. Each patient (or parent/guardian) provided written informed consent.

Statistical analysis

All efficacy (i.e. serum ferritin) analyses were conducted on patients receiving deferasirox from enrollment until change of chelator, death, or loss to follow up. Data were analyzed using the PASW 18.0 for Windows program. Descriptive statistics were expressed as numbers and percentages for categorical variables and as mean, standard deviation (SD), median, and minimum-maximum for numerical variables. In multiple independent group comparisons analysis of variance ANOVA test was used for normally distributed numerical variables and Kruskal-Wallis test was used for non-normally distributed numerical variables. Friedman test was used to assess changes over time for multiple numeric dependent variables whereas Wilcoxon signed-rank test with Bonferroni correction was used for post-hoc comparisons. Spearman's rho (r) test was used for correlation between non-normally distributed numerical variables. A p-value <0.05 was considered statistically significant. Data were analyzed using PASW Statistics 18.0 for Windows (Chicago: SPSS Inc).

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RESULTS

A total of 439 patients were identified to be receiving deferasirox at enrollment. Among these, 415 (94.5%) patients had TDT and 24 (5.5%) had SCA. The age distribution of patients was: 2-6 year (n=143, 32.6%), 7-12 years (n=194, 44.2%), and 13-18 years (n=102, 23.2%). Of note, the mean pre-transfusion hemoglobin level of TDT patients at baseline was 9.1 ± 1.2 g/dL (n=413) which remained stable throughout the study with the mean value after three years being 9.1 ± 1.0 g/dL (n=300) (p=0.673); potentially indicating stable transfusional (iron) intake throughout the study period. Median values were also similar at baseline (9.0 g/dL) and at end of study (9.1 g/dL), indicating that around half of patients were receiving transfusion regimens to target hemoglobin levels lower than the recommended values of 9-10.5 g/dL (1).

Changes in serum ferritin level

Serum ferritin levels in the study cohort consistently and significantly decreased across three years of deferasirox therapy from a median of 1775.5 µg/L (mean: 2063.2 ± 1316.3, min: 112.7, max: 7776) at baseline to a median of 1250.5 µg/L (mean: 1634.9 ± 1272.6, min: 20.6, max: 7421) at end of study ($p < 0.001$) **(Figure 1A)**. Serum ferritin decreases were noted across TDT and SCA patients, and across all three age groups (2-6, 7-12, and 13-18 years) in TDT patients **(Figure 1B)**. In patients with TDT, there was a considerable decrease in the proportion of patients with serum ferritin values >2500 µg/L and a concomitant increase in the proportion of patients with serum ferritin levels <1000 µg/L following three years of deferasirox therapy **(Figure 2A)**.

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Deferasirox dose vs. changes in serum ferritin level

In TDT patients, the mean dose was 26.4 ± 6.1 mg/kg/day. In respective age groups, it was: 26.0 ± 6.2 mg/kg/day (for age 2-6 years, n=137), 27.2 ± 6.0 mg/kg/day (for age 7-12 years, n=182), and 25.4 ± 6.2 mg/kg/day (for age 13-18 years, n=96). Higher mean doses were used in patients with higher baseline serum ferritin levels: 22.9 ± 6.0 mg/kg/day (for baseline serum ferritin <1000 µg/L, n=76), 26.6 ± 6.2 mg/kg/day (for baseline serum ferritin 1000-2500 µg/L, n=213), and 28.0 ± 5.6 mg/kg/day (for baseline serum ferritin >2500 µg/L, n=107). When patients were stratified to dose groups of <20 mg/kg/day (n=33), 20 to <30 mg/kg/day (n=137), and ≥30 mg/kg/day (n=120), a statistically significant difference was noted between groups with regards to serum ferritin change from baseline to end of study (following three years of deferasirox therapy) with the highest change noted in the ≥30 mg/kg/day group (p=0.009) **(Figure 2B)**. The change in serum ferritin every six months over time across the three years of deferasirox therapy was only significant for the ≥30 mg/kg/day group (p <0.001) but not the <20 mg/kg/day (p=0.708) or 20 to <30 mg/kg/day (p=0.170) groups.

Safety

Among 457 patients who received deferasirox at any time during the study (at or post enrollment) and thus evaluated for adverse events, 148 (32.4%) had at least one adverse event reported, 59 (12.9%) had serious adverse events, 6 (1.3%) had adverse events leading to discontinuation (renal tubular disorder n=2, Allogenic bone marrow transplantation therapy n=4), and 8 (1.8%) had adverse events requiring study drug dose adjustment or interruption (hepatic enzyme increased n=6, protein urine present n=1, serum ferritin increased n=1, proteinuria n=1). All of these

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adverse events were reported irrespective of relationship to deferasirox. Only 9 (2.0%) patients had adverse events suspected to be related to deferasirox therapy, the most common being hepatic enzyme increase (n=5, 1 serious), renal tubular disorder (n=2, 1 serious), blood creatinine increased (n=1), abdominal pain (n=1, serious), and protein urine present (n=1).

SCr levels slightly increased across three years of deferasirox therapy ($p < 0.001$), although remaining within normal range. However, ALT levels significantly decreased over three years of deferasirox ($p < 0.001$) (**Figure 3**)**.** There was a significant correlation between serum ferritin level and ALT level at all study visits (every 6 months) (Spearman's [r] range: 0.31-0.47, $p < 0.001$ for all correlations).

DISCUSSION

Our study confirms the long-term efficacy and safety of deferasirox in reducing serum ferritin levels in children with TDT and SCA, and remains the largest clinical cohort in such patients. Deferasirox has been evaluated in randomized clinical trials and showed long-term efficacy in reducing serum ferritin level and safety in children as young as two years of age, with data up to five years of therapy showing no adverse effects on growth or sexual development (12, 13). In these trials, however, children comprised only a subgroup of patients (~50% of study population, 90 patients for SCA and 273 for TDT) with even smaller numbers being evaluated for very young children 2-6 years of age (<10% of population, 5 patients for SCA and 46 patients for TDT) (12, 13). Thus, our study provides confirmation of favorable effects in a large cohort of children including a considerable number of children that are 2-6 years of age (n=143, around one third of patients) who interestingly had the highest

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median serum ferritin levels at baseline, potentially attributed to transfusional rates during critical periods of growth and development.

Serum ferritin levels consistently higher than 2500 µg/L increase the risk of cardiac complications and endocrine disease in TDT (14, 15). In our study, a considerable number of TDT patients shifted from serum ferritin levels >2500 µg/L at baseline to lower levels after three years of deferasirox; thus, putting patients at lower risk of significant morbidity. On the other hand, serum ferritin values <1000 µg/L have been associated with improved survival in TDT (16). Our study has also observed a considerable increase in the proportion of patients with serum ferritin levels <1000 µg/L from baseline to end of study; thus, potentially giving patients the opportunity of more favorable future outcomes. Although iron-related cardiac morbidity is generally absent in patients with SCA, iron overload is still associated with several morbidities including pain crisis, high hospitalization rates, end-organ damage as well as mortality (6-10).

The effect of higher dosing was evident in our study. Although patients were given higher deferasirox doses when they had higher baseline serum ferritin levels, mean values usually remained below 30 mg/kg/day even in patients with serum ferritin levels >2500 µg/L at baseline. The deferasirox dosing recommendation in prescribing information and international guidelines allow escalation up to 40 mg/kg/day in patients with a rising serum ferritin trend >2500 µg/L (1). Appropriate dose selection and adjustment is not only essential for matching transfusional iron intake (17) or adverse event management but also to ensure the iron chelator is given 'its full potential' for reducing iron burden in patients with severe iron overload.

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In deferasirox studies, the greatest median absolute change in serum ferritin levels were observed in patients assigned a starting dose of 30 mg/kg/day (12). Dose escalation during therapy to achieve treatment goals also remains essential. Data from deferasirox studies showed that doses >30 mg/kg/day are needed to reduce iron burden especially in heavily iron overload patients, without additional safety concerns (18, 19).

Only 2% of patients had adverse events suspected to be related to deferasirox therapy and there was no clinically significant change in kidney function which is consistent with data from clinical trials in this patient age group (12, 13). ALT levels not only did not show a significant increase but in fact they significantly decreased over three years of deferasirox. As our study supports that achieving optimal serum ferritin levels of <1000 µg/L may require long-term therapy and with higher doses, it is important to ensure the long-term safety of deferasirox especially at high doses. Data from clinical trials confirm safety of deferasirox for up to 5 years of therapy, including patients as young as two years of age – with no adverse effects noted on parameters of growth or sexual development (12). Data from trials using doses >30 mg/kg/day are also available from trials running up to three years and including patients as young as 2 years of age, confirming its safety (20, 21). Therapy at such doses may be temporary and could be titrated to lower doses once target serum ferritin levels of <2500 µg/L are achieved.

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The main limitation of our study is inability to assess adherence to therapy which may play a role in treatment outcomes including serum ferritin level reductions. It is now established that patient survival and iron removal correlate with adherence to chelation therapy (22), as confirmed in a systematic reviews of 18 published studies (23). In specific, adherence to deferasirox treatment was shown to be higher when compared to subcutaneous deferoxamine, with greater satisfaction and convenience noted in clinical trials (24, 25). Moreover, we were unable to uniformly collect MRI measurements for patients in this study, so we could not evaluate changes in cardiac and hepatic iron levels. Serial serum ferritin measurement, however, is still valuable and recommended for monitoring the efficacy of iron chelation therapy in patients with hemoglobinopathies (1).

The efficacy and safety of deferasirox for managing iron overload in children with TDT and SCA has been confirmed in this largest such cohort to-date, including a considerable proportion of children younger than 6 years. Aside from the need to adjust dosing to transfusional rate, higher drug doses (≥30 mg/kg/day) may be required to ensure significant and higher reductions in serum ferritin level. This remains essential for patients with high serum ferritin levels who remain at higher risk of morbidity and for whom the goal of therapy is achieving a negative balance. The mean pre-transfusion hemoglobin level of TDT patients was ≤9 g/dL after 3-years of follow-up, potentially indicating stable transfusional (iron) intake throughout the study period. Dose adjustment would also be more relevant if transfusion therapy is to be further optimized to achieve recommended hemoglobin levels, as this will translate into a higher ongoing iron intake and accumulation. In order to achieve optimal therapeutic goals, it is important to personalize the treatment through active

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dose adjustments and address potential compliance issues that can arise from multi-year oral treatment.

ACKNOWLEDGEMENTS

The authors thank Khaled Musallam MD, PhD of EVIDA MEDICAL DMCC, Dubai, UAE, for medical editorial assistance. Financial support for medical editorial assistance was provided by Novartis Oncology, Istanbul, Turkey.

CONFLICTS OF INTEREST

DA is an employee of Novartis. The remaining authors have no conflicts of interest to disclose.

SOURCES OF FUNDING

None.

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FIGURE LEGENDS

Figure 1 (A) Serum ferritin level over three years of deferasirox therapy. **(B)** Serum ferritin level at baseline and end of study according to underlying disease and age group. SCA, sickle cell anemia; TDT, transfusion-dependent thalassemia.

Figure 2 (A) Serum ferritin level categories at baseline and end of study in transfusion-dependent thalassemia patients. **(B)** Change in serum ferritin level from baseline to end of study according to deferasirox dose group in transfusion-dependent thalassemia patients. SF, serum ferritin.

Figure 3. (A) Serum creatinine levels and **(B)** alanine aminotransferase levels over three years of deferasirox therapy.

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Figure 1A

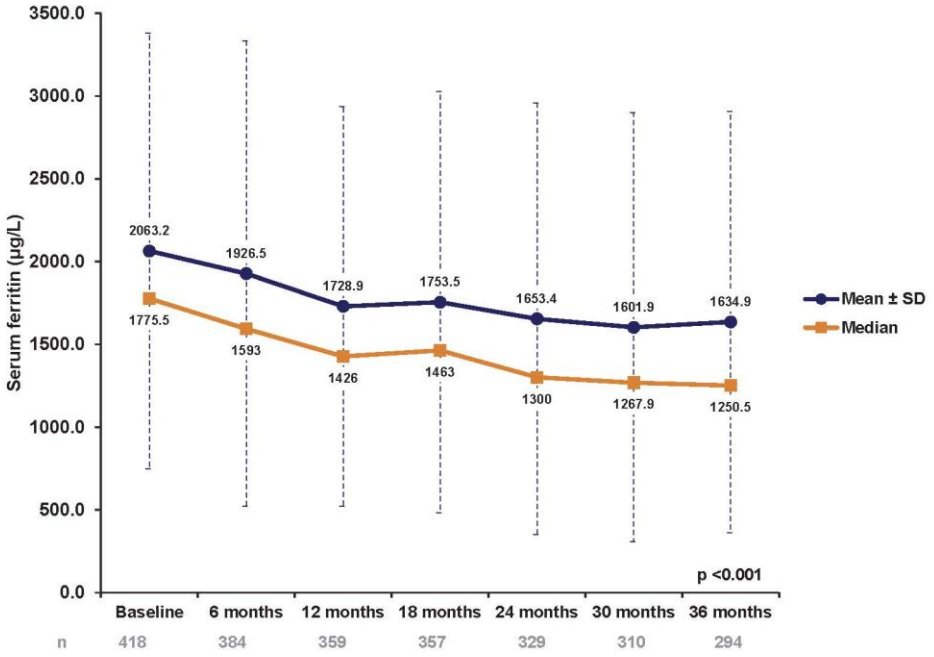
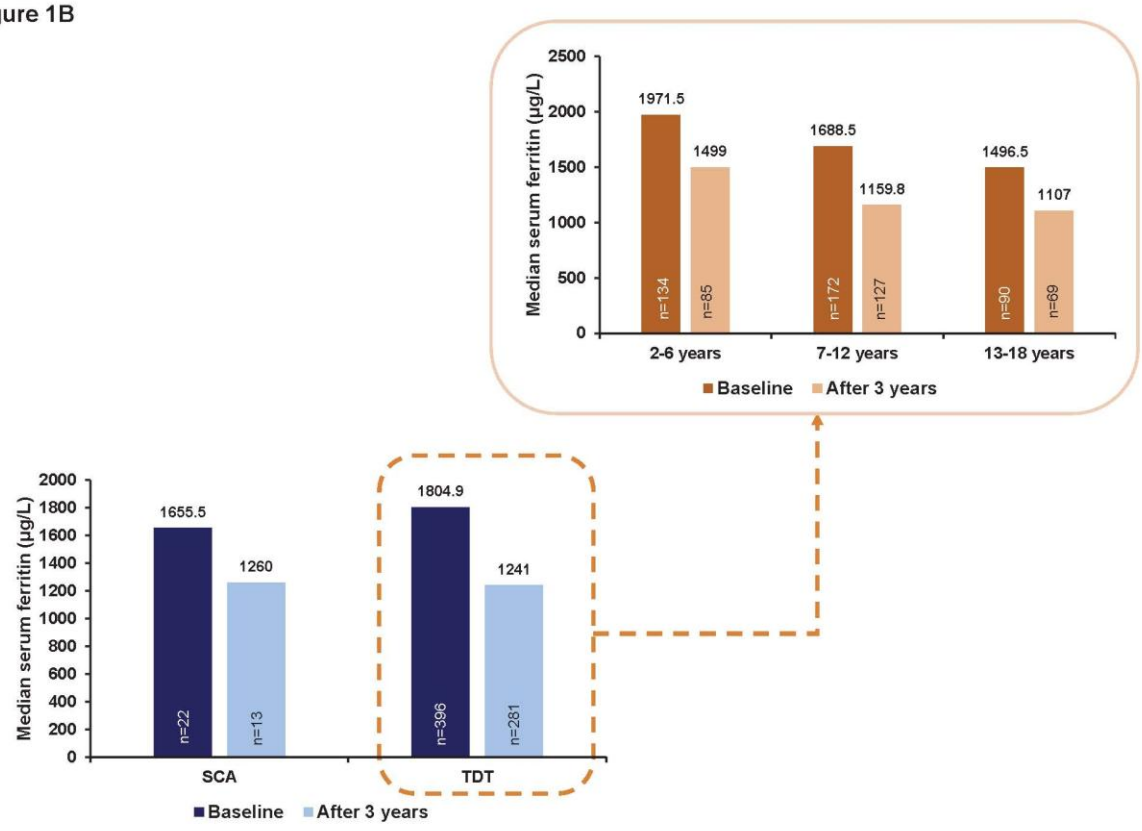


Figure 1B



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Figure 2A

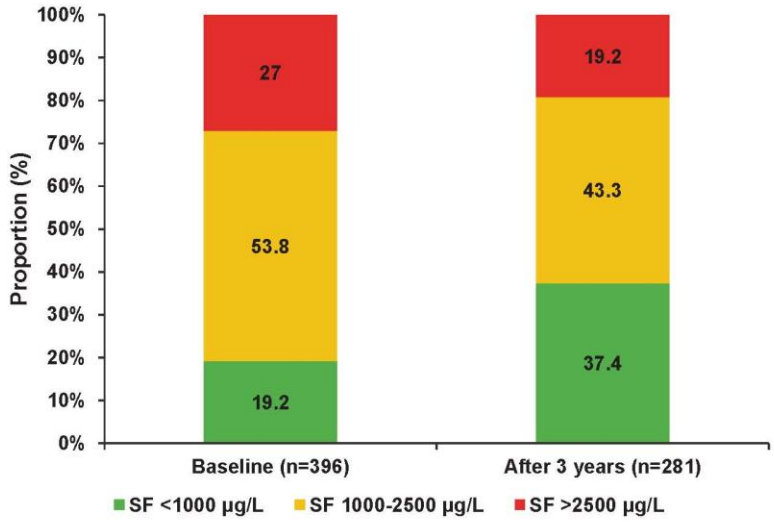
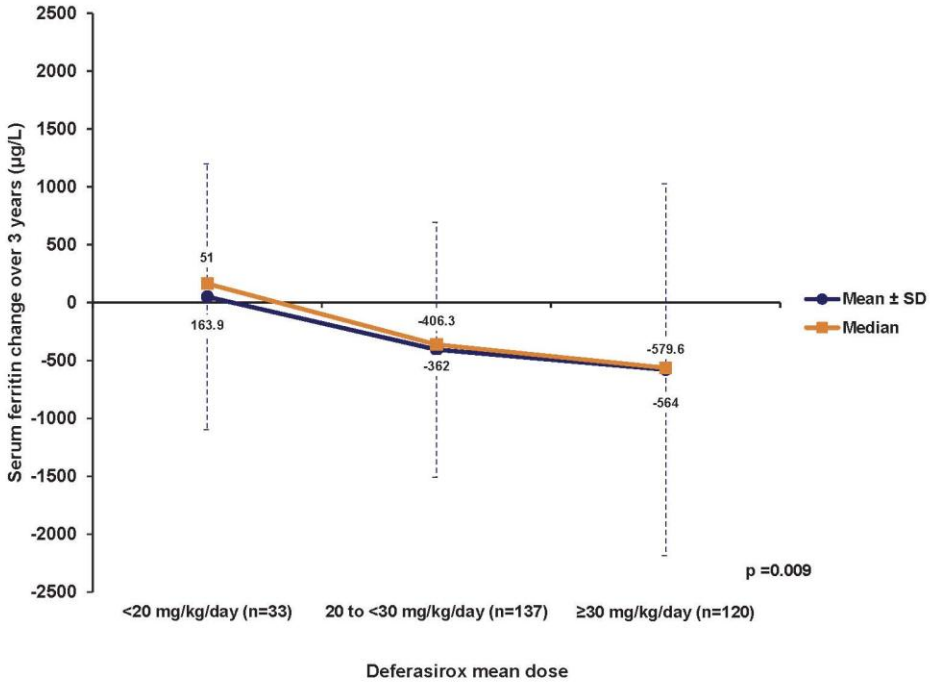


Figure 2B



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Figure 3A

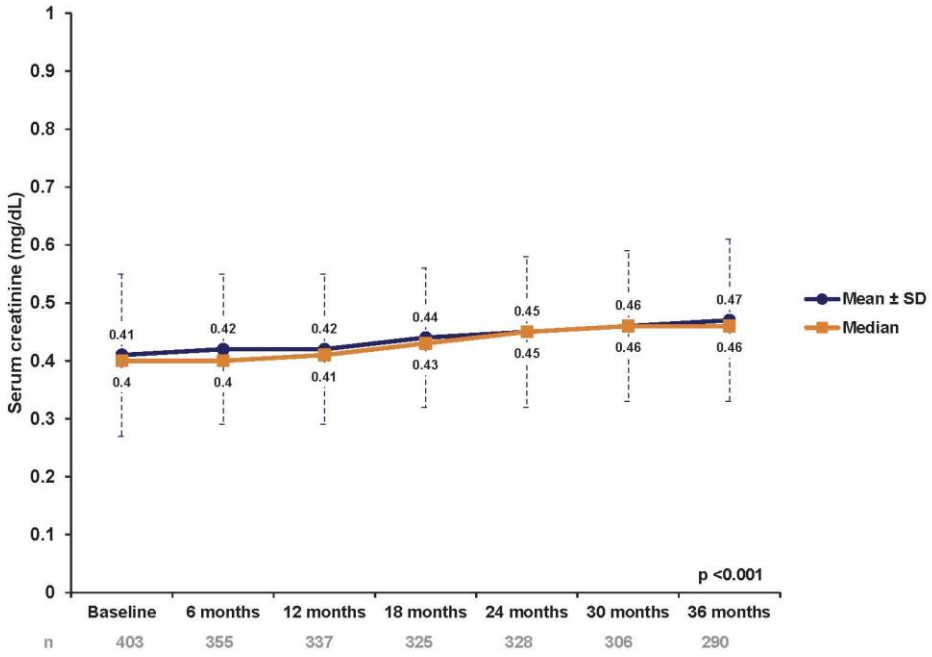
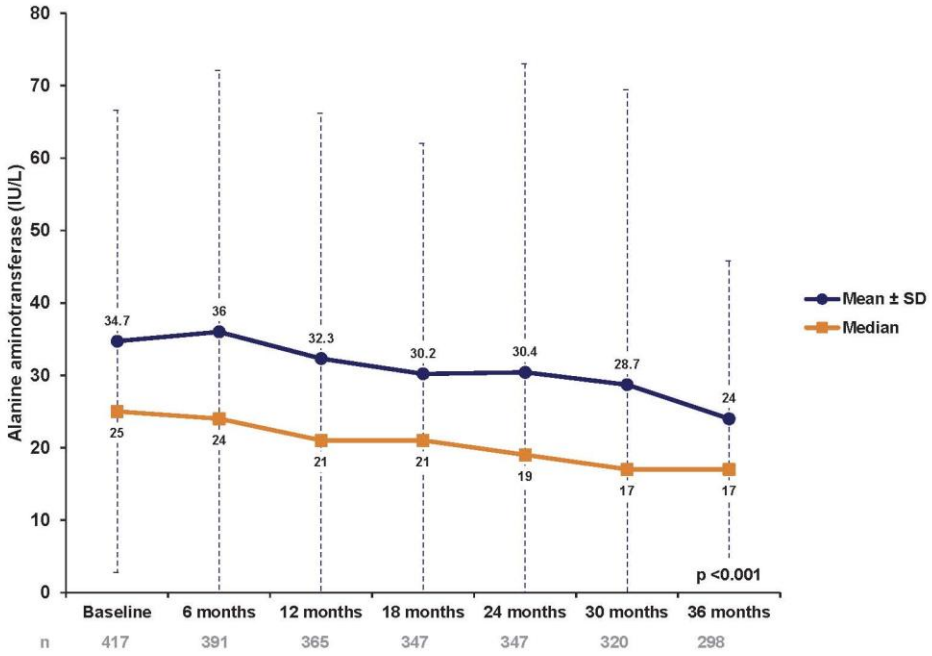


Figure 3B



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