Phase IV open-label study of the efficacy and safety of deferasirox after allogeneic stem cell transplantation

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CV and IJ take the primary responsibility for the paper. The responsible authors of this manuscript confirm that all persons designated as authors quality for authorship, and that each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Running Head: Deferasirox after allogeneic stem cell transplantation

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Abstract:
This is the first prospective study of deferasirox in adult allogeneic hematopoietic stem cell transplant recipients with transfusional iron overload in hematologic malignancies. Patients at least 6 months post-transplant were treated with deferasirox at a starting dose of 10 mg/kg/day for 52 weeks or until serum ferritin was ≤400 ng/mL on two consecutive determinations.

Thirty patients were enrolled and 22 patients completed the study. A significant reduction from baseline in median serum ferritin and in liver iron concentration at 52 weeks was observed in the overall population (1440 to 755.5 ng/mL, $P=0.002$; and 14.5 to 4.6 mg Fe/g dw, $P=0.0007$, respectively). Serum ferritin reduction in patients without deferasirox discontinuation was significantly greater than was found in those who prematurely discontinued the treatment (1541 to 581 ng/mL versus 1416 to 1486 ng/mL, $P=0.008$). Drug-related adverse events, reported in 17 patients (56.7%), were mostly mild to moderate in severity. There were no drug-related serious adverse events. Increase in serum creatinine >33% compared to baseline and greater than the upper limit of normal on two consecutive visits occurred in 12 patients (40.0%). Increase in alanine aminotransferase exceeding 10 x upper limit of normal occurred in 2 patients (6.7%) with active graft versus host disease, both of which resolved. In this prospective study, deferasirox provided significant reduction in serum ferritin and liver iron concentration over one year of treatment in allogeneic hematopoietic stem cell transplant recipients with iron overload. Additionally, the majority of adverse events related to deferasirox were mild or moderate in severity.

Clinical trials identifier: NCT 01335035
Introduction

Management of iron overload in the post-allogeneic hematopoietic stem cell transplant (allo-HSCT) setting may be complicated since the use of therapeutic phlebotomies is often not feasible due to ongoing anemia. Limited but compelling data exist regarding the use of deferasirox in allo-HSCT recipients with beta-thalassemia. [1-6]

Pre-transplant iron overload has been associated with considerable morbidity and increased mortality in patients undergoing HSCT. [7-14] Transfusional hemosiderosis and increased non-transferrin bound iron result in generation of free radicals that may eventually cause oxidative organ damage, especially to the liver, heart and endocrine system. Pre-transplant serum ferritin >1000 ng/mL has been associated with a higher rate of treatment-related complications such as mucositis, acute graft versus host disease (GVHD), liver dysfunction, chronic liver disease, exacerbation of chronic GVHD, hepatic sinusoidal obstruction syndrome (SOS), and bacterial, fungal and viral infections. Elevated serum ferritin levels prior to transplant have been also associated with lower survival rate and increased overall mortality and treatment-related mortality in patients undergoing HSCT for hematologic malignancies. [15] In a study of 112 adults who had undergone allo-HSCT, causes of death within 100 days after transplant among the patients with high serum ferritin were infection (29%), organ failure (29%), GVHD (29%) and SOS (14%). [7] Regarding the effects of persistent iron overload on the long-term morbidity of HSCT survivors, Meyer et al found that, in 290 allo-HSCT recipients, hyperferritinemia had a detrimental effect on post-HSCT survival (0 to 6 months $P<0.001$; 6 to 12 months $P<0.001$; 1 to 2 years $P=0.02$; 2 to 5 years $P=0.002$). [16] However, because serum ferritin is an imperfect surrogate measure of iron stores, its prognostic role in patients with a history of HSCT and iron overload remains to be determined. Several prospective studies have examined the impact of
elevated liver iron concentration (LIC) as measured by magnetic resonance imaging (MRI) on HSCT outcome. To date, there is no consensus regarding the relevance of LIC in HSCT, mainly due to use of different LIC thresholds. [17-21]

We report here on our experience with the prospective use of deferasirox in 30 adults with a variety of hematologic malignancies and transfusional iron overload who survived at least 6 months after allo-HSCT.

**Methods**

Study design

This was an open-label, multi-center clinical trial carried out in Hematopoietic Transplant Units in Spain. Eligible subjects were patients over 18 years of age, who had undergone an allo-HSCT at least 6 months prior to enrollment, with transfusional iron overload (serum ferritin ≥1000 ng/mL or transfusional load ≥20 units [~100 mL/kg] of packed red blood cells), and absolute neutrophil count >1 x 10^9/L. Exclusion criteria included iron overload not related to transfusion, uncontrolled hypertension, active viral hepatitis, human immunodeficiency virus infection, serum creatinine >2 x upper limit of normal (ULN) or creatinine clearance <50 mL/min, significant proteinuria, serum aspartate aminotransferase > 5x ULN, active concomitant malignancies and prior use of iron chelators (supplemental information).

The primary objective of the study was to evaluate the median change in serum ferritin after 52 weeks of treatment with deferasirox in patients with iron overload after allo-HSCT. Secondary objectives were to assess safety of deferasirox, and to explore the use of hepatic MRI to assess LIC.
Deferasirox (initial dose of 10 mg/kg/day) was administered for 52 weeks or until serum ferritin level was ≤400 ng/mL on two consecutive occasions. Dose reductions based on serum ferritin levels and on safety markers (serum creatinine, urine protein/creatinine ratio, liver enzymes, gastrointestinal events, skin rash, hearing loss, ocular alterations, or change in weight) were allowed. An increase in deferasirox dose to a maximum of 30 mg/kg/day was allowed after 3 months if serum ferritin increased or failed to decrease by at least 20% from baseline. Additional chelators, aluminum-based antacids and vitamin C >200 mg/day were not allowed. Assessment of LIC by MRI was performed at selected sites on the basis of availability of equipment. Analysis of MRI images was centrally conducted based on gradient echo sequences. [22] Adverse events were reported by the investigators and recorded in the case report forms. The study protocol was reviewed and approved by local Institutional Review Boards/Ethics Committees. The study was conducted under the Declaration of Helsinki and its amendment. All patients signed informed consent.

Statistical analysis

Categorical variables were described using frequencies and percentages, and quantitative variables by the mean, number of cases, median, standard deviation and range (minimum and maximum). As the distribution was not a normal distribution because the result of Shapiro Wilk normality test for the principal endpoint (serum ferritin) was p<0.05, a non-parametric Wilcoxon test was used for median change in serum ferritin between baseline and after 52 weeks of treatment. Evaluations were performed for the intent-to-treat population. All calculations were performed with SAS for Windows, Version 9.1.3 (Cary, NC, USA). Two-sided tests with a level of significance of 0.05 were used. Safety was assessed in all patients who
received at least one dose of study medication. The intent-to-treat population included patients who had received at least one dose of study medication and had at least one baseline and one post-treatment value of the primary study variable (serum ferritin). For the management of missing values, the last observation carried forward (LOCF) method was used for the principal variable (serum ferritin).

**Results**

**Patients**

Thirty patients were enrolled from December 2008 to April 2010. Eight patients discontinued early, prior to completion of the study, due to: disease progression (3 patients), death (2 patients; one due to disease progression [acute myeloid leukemia] and one due to infection \[Staphylococcus auricularis\] bacteriemia associated with acute respiratory and multiorgan failure]; neither considered related to study drug), drug-related adverse event (1 patient; increased serum creatinine), unsatisfactory therapeutic effect (1 patient), and withdrawal of consent (1 patient, who had mucositis considered to be related to the study drug). The study was completed by 22 patients: 14 after 52 weeks of deferasirox, and 8 who achieved serum ferritin ≤400 ng/mL (x 2 times) before 52 weeks of treatment.

The majority of patients in the series were male (66.7%), and the median age was 46.7 years. Stem cell transplantation was performed for a range of hematologic malignancies, the most common of which was acute myeloid leukemia (n=17) (see Table 1).

At inclusion, the median time since HSCT was 12.2 months (range 6-39 months). The patients had received a mean of 43.5 red blood cell units (range 16-112) before study initiation. Conditioning employed included conventional and reduced intensity regimens. Half of the
patients had an unrelated donor. Stem cell source was bone marrow or peripheral blood in all patients but five in which cord blood was used. Baseline characteristics are summarized in Table 1.

Drug exposure

Overall, patients received deferasirox for a median of 45.7 (range 7.9-57.9) weeks (34.8 [range 8.7-57.9] and 51.4 [range 7.9-56] weeks in patients with baseline serum ferritin <1500 ng/mL and ≥1500 ng/mL, respectively). Doses were increased in 5 patients (16.7%) and reduced in 11 (36.7%). Dose reduction due to increase in serum creatinine occurred in 9 patients (30%), and due to increase in hepatic enzymes in 2 patients (6.7%). Treatment was temporarily discontinued in five patients due to increased liver enzymes (3 patients; 10%), vomiting (1 patient; 3.3%), and hearing disturbances (1 patient; 3.3%). The median time to the first dose adjustment was 15.9 weeks (range 3-44.6). Concomitant use of cyclosporine did not seem to influence the rate of discontinuation of the study drug. Among the 8 patients who discontinued deferasirox, two (14.3%) received concomitant cyclosporine and six (37.5%) did not received cyclosporine.

Deferasirox doses <10 mg/kg/day (median actual dose of 7 mg/kg/day) were received by 7 patients, 10 mg/kg/day by 18 patients, and >10 mg/kg/day (median actual dose of 13.4 mg/kg/day) by 5 patients.

Effect of deferasirox on serum ferritin

A significant reduction in median serum ferritin from baseline to 52 weeks was observed (1444 to 755.5 ng/mL; P=0.002) in the intent-to-treat population (LOCF). Significant decreases in median serum ferritin from baseline were also observed in the 8 patients who met the target value of ≤400 ng/mL (-1030.0 ng/mL; P=0.0078), and in the 14 patients who completed 52
weeks of treatment (-661.5 ng/mL; \( P=0.0134 \)) (Figure 1). Overall, patients without premature discontinuation had a significant decrease in median serum ferritin from baseline (-795.5 ng/mL, \( P<0.0001 \), \( n=22 \)) (Figure 2). The eight patients who discontinued deferasirox prematurely had no change in median serum ferritin from baseline (Table 2 and Figure 1).

The change in median serum ferritin from baseline to week 52 was not significant in the three patients who continued to need red blood cell transfusions during the study (Table 2).

Baseline and final LIC values were available for 7 patients. A significant reduction in median LIC from baseline to 52 weeks was observed (14.5 to 4.6 mg Fe/g dw) (\( P=0.007 \)). Among patients with baseline median LIC <14 mg Fe/g dw, there was a significant decrease from baseline in median serum ferritin at week 52 (1307 to 497 ng/mL, \( P=0.0156 \)). In patients with baseline LIC \( \geq 14 \) mg Fe/g dw there was a non-statistically significant decrease in serum ferritin (2000 to 1528 ng/mL).

Safety

Adverse events were reported in 29 patients (96.7%). Drug-related AEs, reported in 17 patients (56.7%), were mostly mild to moderate in severity (Table 3). Gastrointestinal symptoms (diarrhea, constipation, nausea, vomiting, and anorexia) were the most frequent.

Nine serious AEs were reported in 8 patients (disease progression in 3, and herpes zoster, respiratory infection, febrile syndrome, febrile neutropenia, leukocytosis, and acute massive subdural hematoma in 1 each); none were considered related to the study medication.

Seven patients presented with active GVHD, and 5 with infection at study enrollment (Table 1). During the study, 8 patients (26.7%) had new infectious episodes, and 6 (20.0%) new evidence of GVHD. None of them were considered by the investigators to be related to the study drug.
During treatment, 5 patients presented with increased liver transaminases >4xULN; one had active GVHD at inclusion and two developed new episodes of GVHD through the trial. Two patients, each of whom had active GVHD at inclusion or presented new episodes of GVHD, had an increase in alanine aminotransferase (ALT) >10 x ULN on one occasion. Levels returned to normal in one patient following temporary discontinuation of study drug and study drug was not modified in the second patient who completed 52 weeks of treatment with ALT values <2 x ULN.

Increased serum creatinine >33% compared to baseline on two consecutive visits and >ULN was reported in 12 patients (40.0%); four of the patients had baseline serum creatinine above ULN. The increases in serum creatinine observed in those patients were all < 2xULN.

Fourteen patients (46.6%) were treated with cyclosporine A during the study. There was no statistically significant difference in the incidence of nephrotoxicity in patients according to concomitant use of cyclosporine (5/16 without cyclosporine [31.3%] versus 7/14 patients with cyclosporine [50%]).

Discussion

This is the first report of a prospective study of deferasirox in adult patients with hematologic malignancies who have undergone HSCT. In our study, deferasirox at 10 mg/kg/day administered for 52 weeks post-transplant resulted in a significant reduction in median serum ferritin and mean LIC in 22 adult patients who had undergone HSCT at least 6 months before.

Transfusional iron overload is a relatively common complication in hematological patients and in allo-HSCT recipients. [7, 23] Elevated pre-transplant serum ferritin levels have been associated with increased risk of both overall mortality and treatment-related mortality in patients.
undergoing HSCT, independently of several confounding factors. Elevated serum ferritin has also been associated with increased risk of bacterial infection [7, 8], mucositis [9], acute GVHD [10], chronic liver disease. [11] and SOS. [12, 24] However, because serum ferritin is an imperfect measure of total body iron, the exact prognostic role of iron overload in allo-HSCT remains to be determined. Several prospective studies and a multi-center meta-analysis examined the impact of elevated LIC on HSCT outcomes had different conclusions regarding the prognostic relevance of LIC in HSCT, mainly due to use of different LIC thresholds. [17-21] However, an LIC threshold of >7 mg Fe/g dw has been associated with a decrease in overall survival and non-relapse mortality. [19, 20] In the meta-analysis performed by Armand, there was a trend towards increased non-relapse mortality for LIC>7mg/gdw. [21]

Data from this trial are based on the analysis of absolute change in serum ferritin from baseline. Although the assessment of serum ferritin has limitations (e.g., levels can be increased under infection and inflammation), it is simple and inexpensive and, when assessed serially, generally provides a reliable tool to assess total body iron and response to chelation therapy. In addition, the relationship between long-term control of serum ferritin and survival has been clearly demonstrated in cohort studies of chelated patients with thalassemia major. [25] The use of MRI is becoming more available for measuring iron burden; however, the use of this technique in clinical practice remains limited as the necessary equipment is not widely available. In our study, seven patients had LIC analysis by MRI at baseline, and at the end of the trial.

Initial studies of deferasirox administered following HSCT to patients with transfusional hemosiderosis have been successful. [1-6, 26-30] Two studies in patients with thalassemia; one conducted in children, reported no significant difference in post-treatment serum ferritin levels following deferasirox versus phlebotomy. [1, 4] In children, deferasirox yielded a significantly
decrease in LIC in patients with baseline serum ferritin ≥1000 ng/mL compared to phlebotomy (-8.1 mg Fe/g dw vs -3.5 mg Fe/g dw; \( P=0.048 \)). Notably, parents of 13/14 children randomized to phlebotomy stated a desire for their child to receive deferasirox due to pain, anemia, and hospitalizations. [1] A small retrospective study in patients with hematologic malignancies who had undergone HSCT showed that, while both deferasirox and phlebotomy resulted in statistically significant reductions from baseline in serum ferritin (\( P=0.017 \) and \( P=0.025 \), respectively), the combination resulted in a faster reduction in serum ferritin. [5]

In this study, the majority of patients received 10 mg/kg/day. These doses provided a significant reduction in median serum ferritin from baseline to 52 weeks (1444 to 755.5 ng/mL; \( P=0.002 \)) in the overall population. The starting dose of deferasirox in the majority of the studies in HSCT recipients has been 10 mg/kg/day, lower than that commonly utilized in the non-transplant setting. [1, 4, 27] However, dose adjustment for poor response resulted in doses up to 20 mg/kg/day in some studies. [4, 27] In one study, the mean dose of deferasirox at the last dose was 11 mg/kg/day in the patients with LIC ≤7 mg Fe/g dw and 18.1 mg/kg/day in those with LIC >7 mg Fe/g dw. [1] In our study, the change in median serum ferritin was not significant in three patients who continued to need packed red blood cell transfusions during the study, implying that this subgroup of patients needed higher doses of deferasirox or more time in treatment to show significant decrease in serum ferritin. Also, in patients with baseline LIC ≥14 mg Fe/g dw there was a non-statistically significant decrease in serum ferritin (2000 to 1528 ng/mL). As with the prior subgroup, the patients with higher baseline LIC likely needed a higher dose of deferasirox or a longer duration of treatment.

The safety profile of deferasirox in our study, like in other experiences in HSCT recipients, was similar to that seen in patients with non-malignant transfusional hemosiderosis. [1-6, 26-30] The
most frequent drug-related AEs were increased creatinine levels, increased transaminases, and gastrointestinal symptoms which were generally mild to moderate. [1, 4, 5, 27]

In this report, the increases in serum creatinine were all < 2x ULN. Patients taking cyclosporine did not have a high incidence of increased serum creatinine compared with patients who did not receive cyclosporine. These results are not consistent with a previously published study in patients with aplastic anemia, where significantly more patients taking cyclosporine had increased in serum creatinine >33% above baseline and ULN. However, it should be noted that 56% of patients in that study received deferasirox >20 mg/kg/day. [31].

In our study, two patients, had an increase in alanine aminotransferase >10 x ULN on one occasion. Levels returned to normal in one patient following temporary discontinuation of the study drug and the study drug was not modified in the second patient who completed 52 weeks of treatment with ALT values <2 x ULN. Although transient increase in liver enzymes have been reported as adverse events with deferasirox, a decrease in median alanine aminotransferase over 12 months with deferasirox treatment has also been reported. [4]

The impact of iron chelation on long-term outcomes of patients with iron overload undergoing allo-HSCT has not been evaluated in prospective randomized trials. However, recently published studies analyzed the impact of iron chelation with deferasirox on the patient outcomes. [29, 30, 32] Visani et al have reported eight patients with incomplete hematopoietic reconstitution after HSCT who were treated with deferasirox; all patients experienced an increase in hemoglobin levels followed by transfusion independence. [29] The mechanisms underlying how deferasirox could induce hematologic improvement have yet to be elucidated. Reduction in oxidative stress, a state that has a variety of inhibitory effects on erythroid and hematopoietic function, has been proposed as a possible explanation. [33]
In the study by Sigvin et al, 80 allo-HSCT patients with iron overload were retrospectively analyzed. [30] The patients were divided into two groups: those who did not receive any chelator treatment due to potential side effects or compliance problems and were treated by phlebotomy (group 1), and those who received deferasirox treatment (group 2). In univariate and multivariate analysis, patients in group 1 showed poorer overall survival compared to those in group 2 with an increase in risk of death (HR: 3.22, min–max:1.67–6.23, P = 0.001 and HR: 3.51, min–max:1.75–6.99, P < 0.001; respectively).

A second retrospective study of 158 adult patients who underwent allo-HSCT reported that after a median follow-up of 18 months, the 5-year overall survival probability was significantly higher for patients with serum ferritin <500 ng/mL at the time of transplant than for those with serum ferritin 500-2500 ng/mL or >2500 ng/mL (P=0.002) due to higher transplant related mortality in the patients with serum ferritin >2500 ng/mL (P=0.04). [32] The patients who had received iron chelation had a significantly better overall 5-year survival than non-chelated patients (P=0.008), and experienced significantly less disease relapse (P=0.012).

In conclusion, deferasirox at 10 mg/kg/day administered for 52 weeks post-transplant resulted in a significant reduction in median serum ferritin and median LIC in 22 adult patients who had undergone HSCT at least 6 months before. The majority of adverse events related to deferasirox were mild or moderate, and the safety profile of deferasirox was similar to that reported in previous studies of patients with transfusional hemosiderosis. [2-3]

Additional studies are warranted to determine the exact prognostic role of iron overload in allo-HSCT, and the impact of iron chelation with deferasirox on long-term outcomes in patients with hematologic malignancies and iron overload undergoing allo-HSCT.
Authorship and Disclosure:

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MB and IJ served as investigator coordinators of the trial. LV, CS, AS, RD, CV, DH, JL, MR, SJ, and DV served as principal investigators in the trial. VB interpreted the MRI analysis. All authors contributed to the interpretation of data, reviewed and provided input into the manuscript and approved the final manuscript. MJ supervised the execution of the study, and contributed to the analysis, interpretation, and reporting of the trial data.

DV reports serving as a consultant Novartis and has received speaker honoraria from Novartis. MJ is an employee of Novartis Farmaceutica.

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References


Tables

Table 1. Baseline characteristics of patients (N = 30)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: male</td>
<td>n (%)</td>
<td>20 (66.7)</td>
</tr>
<tr>
<td>Age</td>
<td>median (range)</td>
<td>46.7 (20.3-65.3)</td>
</tr>
<tr>
<td>Hematological disease</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Acute myelogenous leukemia</td>
<td>17 (56.7)</td>
<td></td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td>4 (13.4)</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>2 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia</td>
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<td></td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>1 (3.3)</td>
<td></td>
</tr>
<tr>
<td>Waldenström’s macroglobulinemia</td>
<td>1 (3.3)</td>
<td></td>
</tr>
<tr>
<td>Myelofibrosis</td>
<td>1 (3.3)</td>
<td></td>
</tr>
<tr>
<td>Infused CD34+ cells (x10⁶/Kg)</td>
<td>median (range)</td>
<td>4.0 (0.1-31.0)</td>
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<tr>
<td>Active complications of HSCT at inclusion</td>
<td>n (%)</td>
<td></td>
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<tr>
<td>GVHD</td>
<td>7 (23.3)</td>
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<tr>
<td>Infections</td>
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<tr>
<td>Bacterial</td>
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<td></td>
</tr>
<tr>
<td>Viral</td>
<td>2 (6.7)</td>
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<tr>
<td>Renal function</td>
<td>median (range)</td>
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<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.0 (0.5-1.8)</td>
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<tr>
<td>Creatinine clearance (mL/min)</td>
<td>74.6 (40.0-160.0)</td>
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<tr>
<td>Hemoglobin level (g/L)-median (range)</td>
<td>121 (88-164)</td>
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<tr>
<td>Serum ferritin (ng/mL)</td>
<td>median (range)</td>
<td>1444.0 (788.0-4055.0)</td>
</tr>
<tr>
<td>LIC - median (range) (mg Fe/g dw) (n=14)</td>
<td>14.5 (5.6-19.5)</td>
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### Table 2. Change from baseline in median serum ferritin

<table>
<thead>
<tr>
<th></th>
<th>Baseline (range)</th>
<th>Median Serum Ferritin (ng/mL)</th>
<th>Absolute change (range)</th>
<th>P value(^a)</th>
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<tbody>
<tr>
<td><strong>Overall, ng/mL, n = 30</strong></td>
<td>1444 (788.0 – 4055.0)</td>
<td>755.5 (96.0 – 6128.8)</td>
<td>-670.5 (-2210.0 – 2530.2)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Baseline serum ferritin ng/mL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;1500 ng/mL, n=16</td>
<td>1235 (788.0-1481.0)</td>
<td>448 (96.0-1871.0)</td>
<td>-696.5 (-1124.0 – 883.0)</td>
<td>0.0042</td>
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<tr>
<td>1500-2000 ng/mL, n=6</td>
<td>1760.5 (1675.0-1928.0)</td>
<td>1242 (195.0-1528.5)</td>
<td>-587.5 (-1551.0 – 167.5)</td>
<td>0.0313</td>
</tr>
<tr>
<td>≥2000 ng/mL, n=8</td>
<td>2163.5 (2000.0-4055.0)</td>
<td>1706.5 (650.0-6128.8)</td>
<td>-628 (-2210.0 – 2530.2)</td>
<td>-</td>
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<tr>
<td><strong>Discontinuation of study drug</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No, n = 22</td>
<td>1541 (788.0-4055.0)</td>
<td>581 (96.0-6128.8)</td>
<td>-795.5 (-2210.0 – 2530.2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Yes, n = 8</td>
<td>1416 (809.0-2087.0)</td>
<td>1486 (513.0-2956.0)</td>
<td>-71 (-968.0 – 883.0)</td>
<td>-</td>
</tr>
<tr>
<td><strong>LIC at baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 14 mg Fe/ g dw, n=7</td>
<td>1307 (1119.0-4055.0)</td>
<td>497 (241.0-1845.0)</td>
<td>-1010 (-2210.0 – 604.0)</td>
<td>0.0156</td>
</tr>
<tr>
<td>≥14 mg Fe/ g dw, n=7</td>
<td>2000 (1696.0-3598.6)</td>
<td>1528.5 (195.0-6128.8)</td>
<td>-432 (-1551.0 – 2530.2)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Packed red blood cell transfusions during the study period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No, n= 27</td>
<td>1406.9 (788.0-4055.0)</td>
<td>658 (96.0-6128.8)</td>
<td>-693 (-2210.0 – 2530.2)</td>
<td>0.0018</td>
</tr>
<tr>
<td>Yes, n= 3</td>
<td>1928.0 (900.0-2695.0)</td>
<td>853 (650.0-1280.0)</td>
<td>-648 (-2045.0 – 47.0)</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\) Statistically significant differences found between median serum ferritin at Week 52 and baseline median (Wilcoxon test, P<0.05).
Table 3. Drug-related adverse events (AE)

<table>
<thead>
<tr>
<th>AE</th>
<th>All</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine increase (&gt; 33%)</td>
<td>11 (36.7%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>AST and/or ALT increase</td>
<td>5 (16.6%)</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (6.7)</td>
<td>-</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (3.3)</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (3.3)</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (3.3)</td>
<td>-</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (3.3)</td>
<td>-</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1 (3.3)</td>
<td>-</td>
</tr>
<tr>
<td>Mucositis</td>
<td>1 (3.3)</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Hearing disorder</td>
<td>1 (3.3)</td>
<td>-</td>
</tr>
<tr>
<td>Eye discomfort</td>
<td>1 (3.3)</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> <2 x ULN in all cases
Figure Legends

Figure 1. Median serum ferritin based on continuation or not with study drug
Figure 2. Evolution of change in serum ferritin (+ 25th/75th percentiles)
Figure 1
Figure 2

[Graph showing the median change from baseline in serum ferritin (ng/mL) over time (months).]