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CORRESPONDENCE

Crushed deferasirox film-coated tablets in pediatric patients with transfusional hemosiderosis: Results from a single-arm, interventional phase 4 study (MIMAS)

To the Editor:

Iron overload in transfusion-dependent refractory anemias among pediatric patients is associated with end-organ damage, growth retardation, problems with sexual development, and an increased risk of mortality.[1,2] Treatment adherence is crucial for optimizing long-term iron chelation therapy (ICT) in this patient population, which in turn depends on the mode of administration, frequency of dosing, palatability, and the adverse event (AE) profile of ICT.[1,2] The currently available ICT options include oral deferasirox and deferiprone and the subcutaneously or intravenously administered deferoxamine.[1,2] Deferoxamine and deferiprone are associated with inconvenient dosing schedules and undesirable AEs leading to low compliance, while deferasirox offering once-daily administration is associated with higher adherence.[1–3] However, compliance to deferasirox has been evaluated mostly among adults and adolescents aged >6 years.[3,4]

The ENTRUST observational study that assessed the long-term safety of deferasirox dispersible tablet (DT) in young pediatric patients (aged ≥2 to <6 years) with transfusional hemosiderosis reported a manageable safety profile with no new or unexpected safety findings, and limited discontinuations due to AEs which decreased over time.[5] Yet, the safety and tolerability of deferasirox film–coated tablets (FCT) in patients aged <6 years is not well established, in particular when FCTs are crushed in order to facilitate administration. We conducted the MIMAS study—a 24-week interventional, prospective, single-arm, open-label, phase 4 study (NCT03372083), at 10 sites in 7 countries (Egypt, Italy, Lebanon, Oman, Thailand, the United Arab Emirates, and the United Kingdom)—as a post-authorization measure imposed by the European Medicines Agency to assess the safety, efficacy, patient/caregiver-reported treatment satisfaction, palatability, and gastrointestinal (GI) symptoms with crushed deferasirox FCT among pediatric patients aged ≥2 to <6 years with transfusional hemosiderosis and a documented history of red blood cell transfusions.

The study included a 14-day screening period to assess patient eligibility, a treatment duration of 24 weeks, followed by a 30-day safety follow-up. All patients underwent weekly monitoring of renal function and biweekly assessments for hepatic function during the first month. Thereafter, safety assessments were performed every 4 weeks, including the monitoring of serum ferritin (SF) levels. Patients on prior deferasirox treatment were included if their baseline SF levels were >500 μg/L and if they received a daily dose of deferasirox equivalent to FCT ≥7 mg/kg/day. Patients on prior ICT other than deferasirox or those who were ICT-naïve were included if their SF was >1000 μg/L. Patients who previously received >1 ICT, who were continuing treatment with other ICTs, with unresolved AEs from prior ICTs, or with significantly impaired GI function or GI disease that could alter the absorption of the drug, were excluded.

Crushed deferasirox FCT dosing was based on body weight; dose modification was permitted. The starting dose was calculated depending on patients' prior history of ICT use: ICT-naïve or prior deferasirox DT or any other iron chelator. For patients on deferoxamine and deferasirox DT, the starting dose for crushed deferasirox FCT was calculated based on a standardized conversion of prior ICT to deferasirox FCT. The targeted starting dose was 14 mg/kg/day, with a minimum dose of 3.5 mg/kg/day and maximum dose of 28 mg/kg/day. The full daily dose of deferasirox FCT had to be crushed in the home environment and administered by sprinkling on soft food to be consumed immediately.

The primary objective was to assess the safety of crushed deferasirox FCT with respect to protocol-defined selected GI disorders (esophagitis, stomatitis, mouth ulceration, gastric ulcers, hemorrhage, abdominal pain, diarrhea, nausea, and vomiting) for up to 24 weeks (plus an additional 30 days of follow-up). Secondary objectives included evaluation of treatment-related AEs (TRAEs); frequency and severity of AEs, serious AEs (SAEs), AEs leading to discontinuation, and absolute change from baseline in hematology and biochemistry parameters; assessment of efficacy based on change over time in SF levels from baseline; and evaluation of treatment satisfaction, palatability, GI symptoms, adherence and concerns of patients/caregivers based on patient-reported outcome (PRO) questionnaires: Palatability, GI symptom, and modified Satisfaction with Iron Chelation Therapy (mSICT). The study was conducted in accordance with the ICH E6 Guideline for Good Clinical Practice and informed consent was obtained from caregivers or legal guardians of the patients.

Of 44 patients enrolled (median age, 3.0 years; range, 2.0–5.0 years), most patients had β-thalassemia major (35 [79.5%]), 3 patients (6.8%) had hemoglobin E/β-thalassemia, and 1 patient each (2.3%) had pure red cell aplasia and congenital aplastic anemia reported. In the remaining 4 patients, the precise underlying medical condition for chronic transfusion was not reported. Overall, 34 patients (77.2%) had received prior ICT (32 patients with deferasirox). The median SF level at baseline was 1906.5 μg/L (range, 570.0–5020.0 μg/L). The median duration of exposure to crushed deferasirox FCT was 23.0 weeks (range, 5.1–26.0 weeks). The mean dose intensity was 19.09 mg/kg/day; the mean

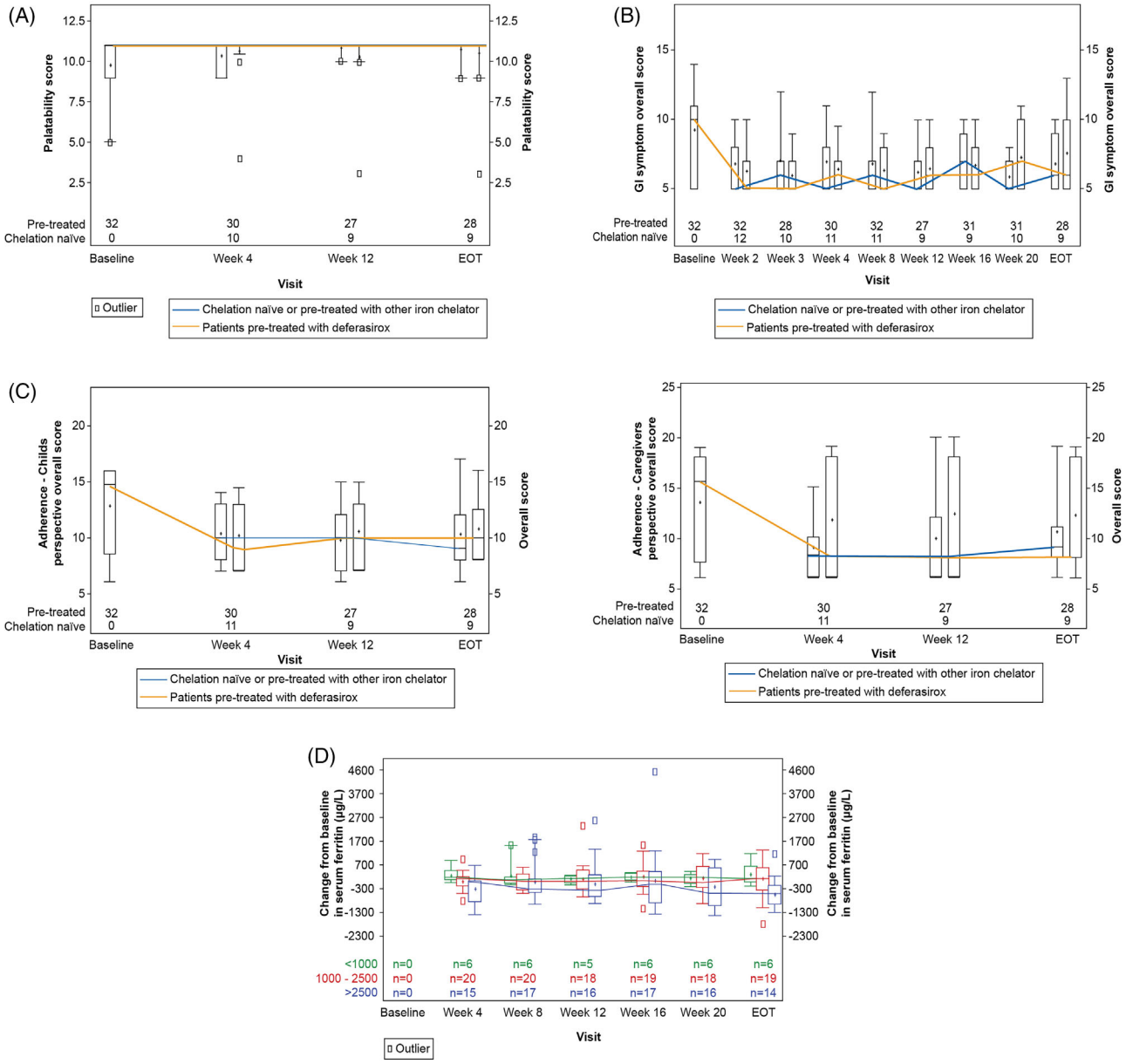

FIGURE 1 Overview of palatability, GI symptom and adherence scores, and SF levels. (A) Box plot of scores by time point for palatability; (B) Box plot of scores by time point for GI symptom scores; (C) Box plot of scores by time point for mSICT observer-reported outcome (ObsRO) (FAS) – Adherence (child's and caregiver's perspective); (D) Box plot of change from baseline by time point in SF levels (FAS). Distribution of SF levels at baseline: 0 to ≤1000 µg/L: 6 patients; >1000 to ≤2500 µg/L: 21 patients; >2500 µg/L: 17 patients. Number of patients mentioned above x axis at each time point represent the number of patients based on whose data the boxplots were created. In figures A,B and D, the length of the box represents the interquartile range (the distance between the 25th and 75th percentiles); the whiskers extend to the 10th and 90th percentile. The means are presented as dots, and the medians of time points are connected over time. EOT, end of treatment; FAS, full analysis set; GI, gastrointestinal; mSICT, modified Satisfaction with Iron Chelation Therapy; SF, serum ferritin

cumulative dose was 2964.81 mg/kg. Seven patients (15.9%) experienced a protocol-defined selected GI disorder; diarrhea was most frequent (4 [9.1%]), followed by abdominal pain (2 [4.5%]) and vomiting (2 [4.5%]). None of the other selected GI disorders specified in the protocol were reported.

Overall, 31 patients (70.5%) experienced ≥1 AEs; most AEs were mild or moderate. SAEs requiring hospitalization were reported in 2 patients (4.5%) (pyrexia and bronchiolitis; not treatment-related). No deaths occurred during the study. TRAEs were reported in 22 patients (50.0%); 2 patients (4.5%) had severe TRAEs (increased liver function test parameters and increased urine protein/creatinine ratio). Increased urine protein/creatinine ratio was reported in 12 patients (27.3%), of which 6 required dose adjustment/interruption. In total, treatment discontinuation due to TRAEs was needed in 3 patients

(6.8%). No serious TRAEs were observed. There were no clinically relevant changes in white blood cells, neutrophils, and platelet counts; particularly, no AEs of cytopenia were reported. The trends for alanine aminotransferase, aspartate aminotransferase, total and direct bilirubin, creatinine, and protein/creatinine ratio remained stable over time. There was no indication of progressive worsening of renal function over time. No significant audiovisual AEs and electrocardiogram results were reported.

PRO outcomes were similarly positive in both deferasirox pre-treated and deferasirox-naïve patients. Palatability was rated as "good" by most patients (score range, 10.3–10.9 from a maximum possible score of 11, which indicated best palatability). GI issues were not considered a major concern; from week 2 onwards, the post-baseline mean GI symptom score was consistently below 10 (from a maximum possible score of 25, which indicated worse GI symptoms) (Figure 1A,B).

The mSICT questionnaire showed that mean adherence scores trended toward improvement from both children and their caregivers' perspectives (Figure 1C). Efficacy analysis showed a slight reduction (−6.6%) in mean (standard deviation) SF levels from 2130.1 (1077.15) at baseline to 1989.4 (963.15) μg/L at week 24 (Figure 1D). Stratification according to baseline SF levels showed a higher reduction of SF in patients with SF ≥2500 μg/L, with an average reduction of 17.4% at week 24.

The major limitations identified in this study were the single-arm design, relatively short 24-week study duration, and moderate sample size. In addition, a substantial proportion of the patients were pretreated with deferasirox, leading to a possible selection bias toward patients who had better tolerability to the drug.

The MIMAS study demonstrated good GI tolerability of crushed deferasirox FCT in children. Overall, the safety profile was consistent with that reported previously.[3,5] AEs were mostly mild or moderate and the TRAEs resolved with dose adjustment or temporary ICT interruption. Therapy-related discontinuations were low with no reported mortality. The overall safety findings of this study are aligned with those of the ENTRUST observational study that showed good tolerance of deferasirox DT in pediatric patients.[5] In MIMAS, the analyses of the PRO data revealed an overall favorable patient satisfaction with crushed deferasirox FCT with decreased concerns regarding palatability and GI symptoms and improved treatment adherence in children aged <6 years. The efficacy findings in MIMAS are in line with previous reports. The trend of SF reduction was consistent with that of ECLIPSE—a 24-week, randomized study, which compared deferasirox FCT with the DT formulation in transfusion-dependent patients aged ≥10 years.[3] It is expected that with longer follow-up, further reduction in SF levels will be observed. In ECLIPSE, a trend toward a higher reduction in SF from baseline to week 24 and a more favorable profile for PROs was observed in FCT-treated versus DT-treated patients,[3] which was corroborated by a recent analysis that showed that PROs (adherence, satisfaction, concerns, palatability scores, and frequency of severe GI-related AEs) together mediated 90.1% of the association between treatment formulation and reduction in SF levels ($p<0.05$).[6] These data suggest that PRO scores, specifically adherence, represent important mediators of the observed difference in SF reduction between FCT- and DT-treated patients.[3,6]

The current findings support earlier evidence, which suggest that regardless of age and underlying disease, patients prefer the once daily deferasirox FCT formulation as it improves patient satisfaction and treatment adherence.[4] On the basis of the MIMAS study, crushed deferasirox FCT seems a reasonable treatment option for young children, which may lead to higher treatment satisfaction, adherence, and optimal efficacy.

AUTHORS CONTRIBUTIONS

All the authors contributed to designing and performing the research, manuscript writing, reviewing it critically, and approving the submitted version.

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CONFLICT-OF-INTEREST

Wali Y received research grants and honoraria from Takeda, Novo Nordisk, Pfizer, and Novartis. Shared in advisory boards for Takeda, Pfizer, and Novartis. **Tartaglione I** reported consultancy for bluebird bio and honoraria from Celgene and Novartis; **Origa R** reported speakers' bureau fees from Novartis and membership of the advisory committee for bluebird bio and Novartis; **Miguel I, Socrates O, and Tania R** are employees of Novartis; **Taher A** provided consultancy and received research funding from Novartis Pharmaceuticals, Bristol-Myers Squibb, Imara, Vifor, IONIS Pharmaceuticals and provided consultancy to Agios. **Hassan T, Charoenkwan P, Trompeter S, Gamberini MR, and Viprakasit V** declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was conducted according to ICH E6 Guideline for Good Clinical Practice.

INFORMED CONSENT

Informed consent was obtained from each patient's caregiver(s) or legal guardian in writing before screening and before performing any study-specific procedure. Investigators also sought to obtain patient assent according to local, regional, or national regulations.

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