Compliance and clinical benefit of deferasirox granule and dispersible tablet formulation in pediatric patients with transfusional iron overload: in a randomized, open-label, multicenter, phase II study

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Abstract

CALYPSO (*clinicaltrials gov. Identifier: NCT02435212*), a randomized, open-label, multicenter, phase II study evaluated the compliance, clinical benefits, and safety of deferasirox granules and dispersible tablets (DT) in pediatric patients with iron overload. Iron chelation therapy-naive and iron chelation therapy-pretreated patients aged 2 to <18 years with transfusion-dependent anemias were enrolled. Patients were randomized 1:1 to deferasirox granules or DT for 48 weeks, stratified by age group and prior iron chelation therapy. In this study, the co-primary objectives are to evaluate compliance and change from baseline in serum ferritin after 24 weeks for both formulations in iron chelation therapy-naive patients. In total, 224 patients, mostly with β-thalassemia major (63.4%), were randomized to granules (N=112) or DT (N=112). Primary analysis was conducted when 96 iron chelation therapy-naive patients had completed 24 weeks of treatment/discontinued early; least squares mean (LSM) compliance in the deferasirox granules and DT groups, was 86.8% and 84.3% (difference 2.6%; *P*=0.360) respectively, while least squares mean change from baseline in serum ferritin was +4.8 and -171.5 ng/mL (difference: 176.4 ng/mL; *P*=0.255). Slight differences were observed in the observer/patient-reported outcome scores between the granule and dispersible-tablet groups and the overall scores indicate good adherence, satisfaction/preference, fewer concerns and good palatability with both deferasirox formulations. Safety analyses (N=221) found that the most frequently observed adverse events (granules and DT) were increased urine protein/creatinine ratio (>0.5 mg/mg; 24.5% and 34.2%), upper respiratory tract infection (28.2% and 29.7%), and pyrexia (26.4% and 23.4%). In iron chelation therapy-naive patients, mean compliance and change from baseline in serum ferritin with both deferasirox formulations were not significantly different. The safety profile was comparable between granule and DT formulations, and was consistent with the general safety profile of deferasirox.

Introduction

In pediatric patients with transfusion-dependent hemoglobinopathies, such as thalassemia and sickle cell disease, iron chelation therapy (ICT) is an important part of supportive care owing to the risk and consequences of iron overload, including hypogonadism, growth retardation, organ dysfunction, cardiomyopathy and arrhythmias, and increased mortality.[1-4] Currently, three main iron chelators are commonly used: deferoxamine, deferiprone, and deferasirox. The once-daily oral deferasirox dispersible-tablet (DT) formulation, available since 2005, has a well-defined safety and efficacy profile in pediatric patients with transfusional iron overload[5-7] and offers an alternative option with greater compliance over parenteral deferoxamine.[8-10] However, the DT formulation has been associated with compliance issues due to palatability and gastrointestinal (GI) tolerability, which are important factors for appropri-

ate administration and compliance with ICT, particularly in pediatric patients.[10,11] Compliance with ICT can have an impact on iron overload-related consequences, organ dysfunction, and survival.[12-14]

Deferasirox film-coated tablet (FCT) and granule formulations were developed to improve palatability, tolerability, and patient compliance. Both formulations contain the same active substance as the DT formulation (strength-adjusted to maintain comparable DT dosage), but are lactose and sodium lauryl suphate-free and can be taken with a light meal.[15] Granules (sprinkled onto soft food, e.g., yogurt) are convenient for pediatric patients unable to swallow the FCT.[15]

The phase II CALYPSO study (*clinicaltrials gov. Identifier: NCT02435212*) was designed to evaluate the compliance and clinical benefit of deferasirox granules and deferasirox DT, in addition to assessing palatability/treatment satisfaction and safety in pediatric patients with transfusional iron overload.

Methods

Study design

CALYPSO is a randomized, open-label, multicenter (37 sites in 17 countries), two-arm, phase II study (*Online Supplementary Figure S1*). The study was initiated on October 21, 2015. The key changes that occurred after the commencement of the study are listed in the *Online Supplementary Table S1*. ICT-naive and ICT-pretreated patients aged 2 to <18 years with transfusion-dependent anemias and a history of transfusion of ~20 packed red blood cell units and serum ferritin (SF) level >1,000 ng/mL at screening visits 1 and 2, requiring ICT owing to iron overload, were enrolled. Patients were randomized 1:1 to receive treatment with deferasirox DT or deferasirox granules for a 48-week core treatment phase. Randomization was stratified based on age (2 to <10 years or 10 to <18 years) and prior ICT (yes/no). Patients who benefit from the granules or DT in the core phase may continue to the optional extension phase where the patients would be provided with granules for up to 5 years or until they have local access to the granules or FCT.

Deferasirox is available in three dosing strengths for each formulation (DT: 125, 250, and 500 mg; granules: 90, 180, and 360 mg); dose calculations are based on the patient's weight. The deferasirox granules' dose was strength-adjusted owing to higher bioavailability compared to DT. ICT-naive patients started on deferasirox DT 20 mg/kg/day or granules 14 mg/kg/day, with adjustment after 4 weeks based on SF levels. ICT-pretreated patients underwent a 5-day chelation washout period prior to commencement of study treatment. Their starting dose corresponded to their closest prewashout dose, with adjustments every 3 months as needed.

This study was conducted in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki and was approved by independent ethics committee or institutional review board at participating sites (*Online Supplementary Table S2*). Patients (or parents/guardians) provided written informed consent prior to enrollment.

Outcomes

The primary objective of the study is to evaluate deferasirox granules or DT formulations on patient compliance and change from baseline in SF levels over 24 weeks of treatment in ICT-naive patients during the core phase. The co-primary endpoints are patient compliance (using stick pack/tablet count) and change from baseline in SF levels, both evaluated over 24 weeks of treatment in ICT-naive patients with deferasirox granules or DT formulations.

Secondary endpoints include change from baseline in SF levels and compliance after 48 weeks in ICT-naive, ICT-pretreated patients and all patients; patient/observer-reported outcome (PRO/ObsRO) assessments using questionnaires for domain scores for treatment satisfaction (modified Satisfaction with Iron Chelation Therapy [mSICT]) and palatability in all patients; compliance using a daily PRO/ObsRO questionnaire, assessing the rate of dosing instruction deviations (doses missed or not taken at the same time every day); and overall safety (adverse events [AE], laboratory values, vital signs, physical, ophthalmological, audiometric, cardiac, and growth and development evaluations). Pre-dose and post-dose pharmacokinetic (PK) data are also assessed to support the assessment of compliance and exposure-response relationships for measures of safety and effectiveness.

In this article, we report the primary and secondary outcomes in pediatric patients with iron overload.

Statistical analysis

Descriptive statistics were used to summarize the continuous data. Intention-to-treat principle was used to analyze the results. Co-primary endpoints (patient compliance and change from baseline in SF levels) were evaluated using ANCOVA model in ICT-naive patients where significant results (at a one-sided 5% level) had to be shown for both endpoints for the trial to meet the primary objective. The data from the completed core phase (data cutoff of January 18, 2021) were summarized. Secondary efficacy endpoints were assessed in ICT-naive, ICT-pretreated, and all randomized patients during the core phase; patients in each of these three analyses sets who received at least one dose of study drug were included in the safety analysis. Patients with at least one evaluable pre-dose or 3 hours post-dose PK concentration (deferasirox) were included in the PK analysis set. Descriptive analysis was used to analyze adverse events. Further details are described in the *Online Supplementary Appendix*.

Results

The primary analysis was performed when approximately 96 randomized ICT-naive patients had completed 24 weeks of treatment/discontinued early (data cutoff of May 31, 2018). The primary endpoint and PK assessments used this data cutoff.
Additional analyses were conducted at the end of the core phase (data cutoff of January 18, 2021). The data for secondary endpoints and safety assessments from all patients who completed or discontinued the treatment in the core phase used this data cutoff.

Patient disposition and demographics

A total of 224 patients (overall patient population) were randomized into deferasirox DT or granules treatment arms (N=112 in each treatment arm). When stratified by prior ICT treatment, the overall patient population was divided into ICT-naive (N=108; 54 in each treatment arm) and ICT-pretreated patients (N=116; 58 in each treatment arm). The safety analysis included 221 patients (DT: N=111; granules: N=110); three patients were randomized and not treated. The reasons for not receiving treatment include protocol deviation, consent withdrawal prior to treatment initiation, and lost to follow-up. Patient disposition for the overall patient population at the end of the core phase is shown in Figure 1. Overall, 186 patients (83.0%) completed the core phase, and 38 patients (17.0%) discontinued. Treatment discontinuation was reported in 11.6% and 22.3% of patients receiving deferasirox granules and DT, respectively. The main reasons for discontinuation in both arms were AE and withdrawal by parent/guardian. The main reasons for parent/guardian withdrawal included the inability or difficulty to comply with study visit/procedures schedules, wish to change to another iron chelator and/or combination therapy, personal reasons or decision to discontinue treatment.
The majority of patients in the overall, ICT-naive, and ICT-pretreated patient populations were aged between 2 and <10 years (81.7%, 92.6%, and 71.6%, respectively). The median age of patients in the overall, ICT-naive, and ICT-pretreated patient populations was 5 (range, 2-16), 2 (range, 2-13), and 7.5 (range, 2-16) years. The majority (63.4%) of patients in the overall population had β-thalassemia major as the underlying condition for transfusion (Table 1).

Deferasirox exposure for core phase

In the overall patient population, the majority of patients in both treatment groups (90.0% and 78.4% in the deferasirox granules and deferasirox DT groups, respectively) had study drug exposure of ≥44 weeks, and the median duration of exposure was similar in deferasirox granules and deferasirox DT groups (337 and 336 days respectively). The mean (standard deviation [SD]) deferasirox doses received were 18.0 (4.1) and 25.1 (6.7) mg/kg/day in patients receiving granules and DT, respectively (Table 2).
In the ICT-naive patients, an exposure of ≥44 weeks was observed in 94.2% and 79.6% of patients in the deferasirox granules and deferasirox DT groups, respectively, and the median duration of exposure was similar in the deferasirox granules (337.0 days) and deferasirox DT groups (336.5 days).
Efficacy and safety results for the ICT-pretreated patient population are described in the *Online Supplementary Appendix*.

Efficacy

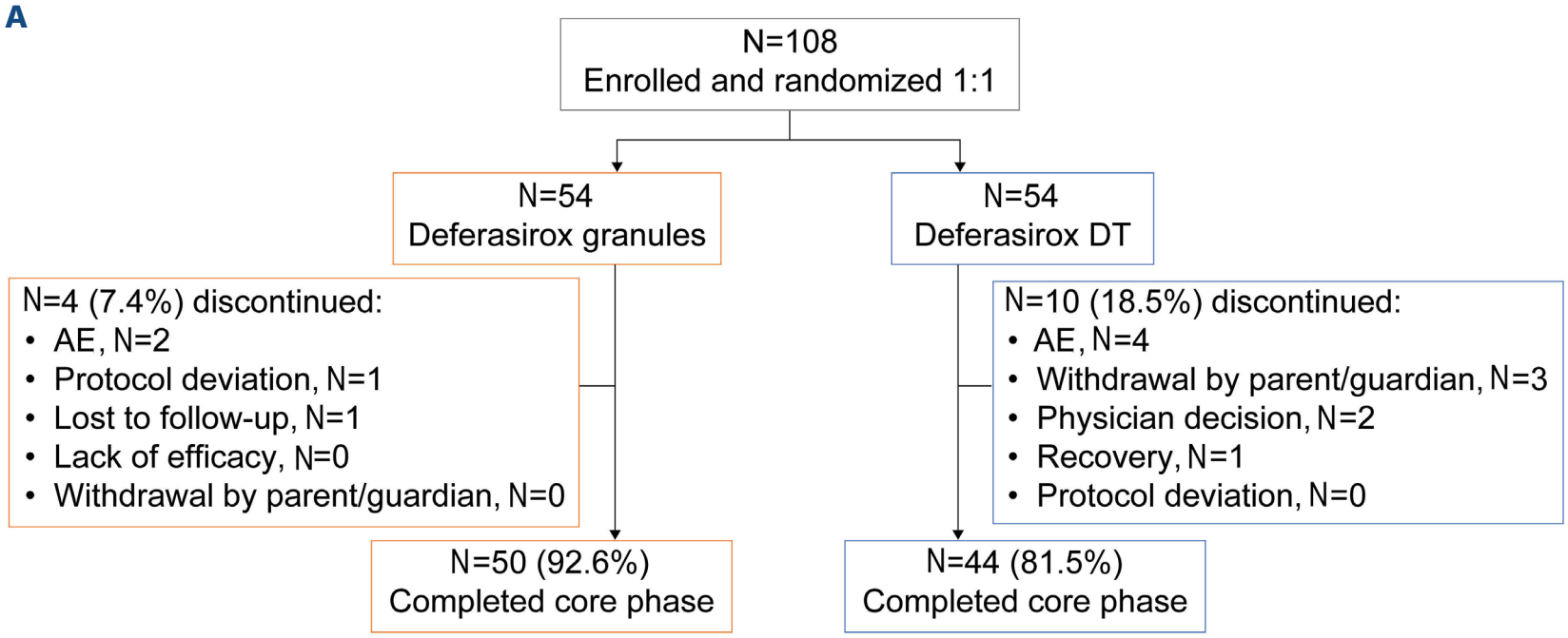
Co-primary endpoint

Based on the ANCOVA model, the least squares mean (LSM) compliance after 24 weeks for ICT-naive patients in the deferasirox granules (N=54) and deferasirox DT (N=54) groups, respectively, was 86.8% (standard error [SE]: 3.0; 95% confidence interval [CI]: 80.9-92.8) and 84.3% (SE: 3.1; 95% CI: 78.2-90.4) (Figure 2A). The difference between the treatment groups was not statistically significant (2.6% [SE: 2.8; 95% CI: -3.0 to 8.2; *P*=0.360]).
The LSM (SE) changes from baseline in SF after 24 weeks for ICT-naive patients in the deferasirox granules and deferasirox DT groups, respectively, were 4.8 ng/mL (SE: 170.6; 95% CI: -333.6 to 343.3) and -171.5 ng/mL (SE: 174.4; 95% CI: -517.4 to 174.4) (Figure 2B). The difference between the treatment groups was not statistically significant (176.4 ng/mL [SE: 153.9; 95% CI: -129.0 to 481.7; *P*=0.255]).
The study objective based on the co-primary endpoints of patient compliance and change from baseline in SF in the ICT-naive patients after 24 weeks of treatment was therefore not met. The results of the compliance and SF changes from baseline analyses repeated in the overall patient population were similar to those of the ICT-naive patients (Figure 2).
After stratification by baseline SF levels (≤1,500, >1,500-2,500, and >2,500 ng/mL; *Online Supplementary Figure S2*) in ICT-naive patients, mean SF changes from baseline to the end of the treatment core phase were comparable between both treatment groups. A similar pattern was observed in the overall patient population.

Secondary efficacy endpoints

Figure 3A shows the mean compliance for deferasirox granules and deferasirox DT for the ICT-naive and overall populations after 48 weeks. After 48 weeks, the mean (SD) compliance in the ICT-naive, ICT-pretreated and overall populations, respectively, was 94.8% (11.9%), 90.4% (12.7), and 92.5% (12.5%) for deferasirox granules (N=52, N=58, and N=110, respectively), and 91.6% (14.4%), 87.1% (18.0), and 89.2% (16.4%) for deferasirox DT (N=54, N=58 and N=112, respectively).
Figure 3B shows the mean change from baseline in SF for deferasirox granules and deferasirox DT for all patient

A



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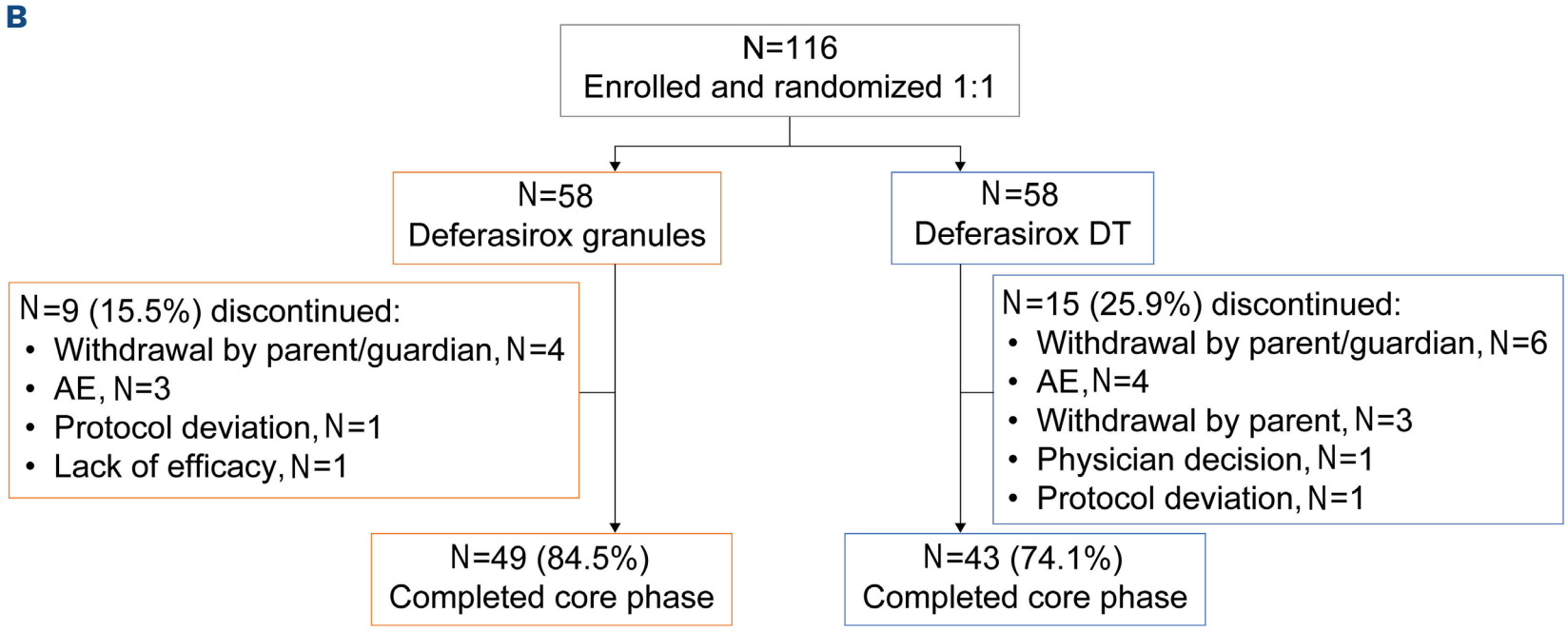

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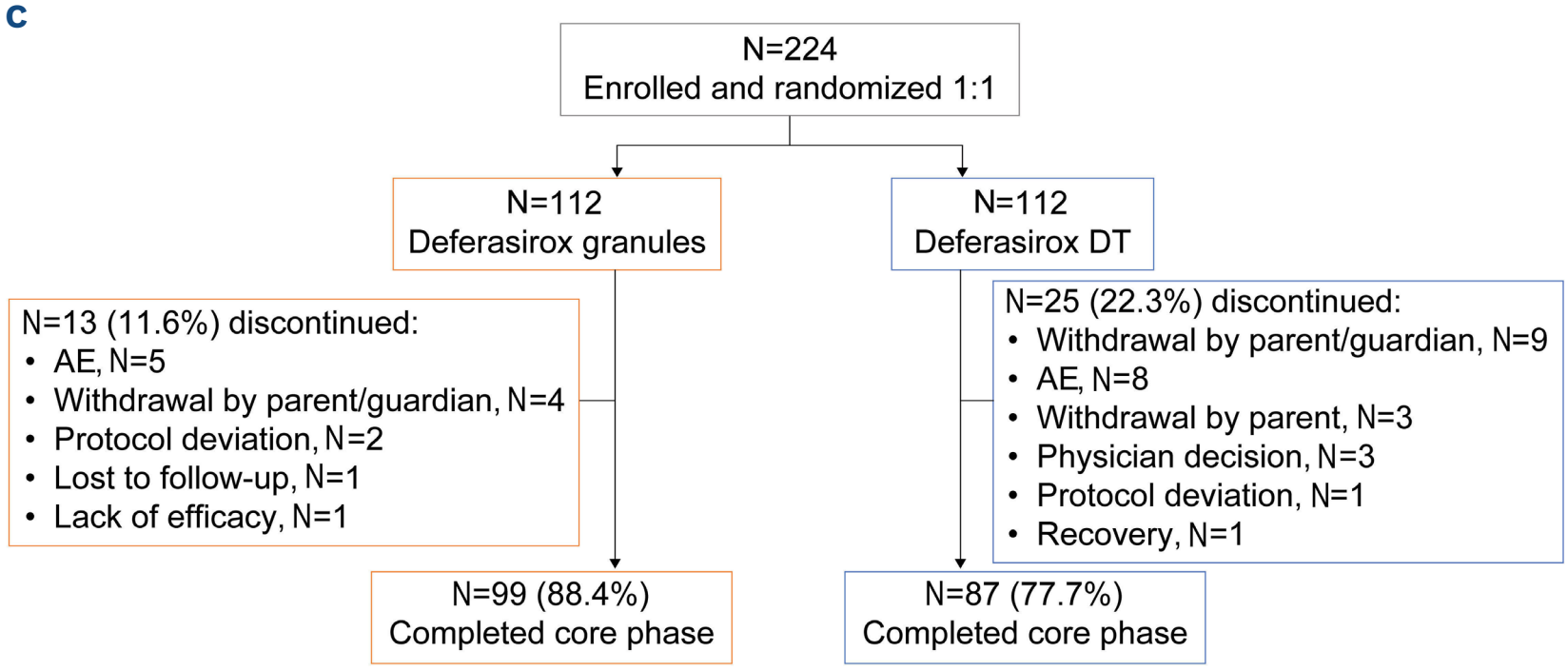

Figure 1. Patient disposition. (A) Iron chelation therapy-naive (ICT-naive)*; (B) ICT-pretreated**; (C) all patients***. Based on January 18, 2021 cutoff date; *2 patients were randomized and not treated; **1 patient was randomized and not treated; ***3 patients were randomized and not treated. AE: adverse event; DT: dispersible tablet; ICT: iron chelation therapy.

Table 1. Patient demographics and baseline characteristics.

	ICT-naive patients, N (%)			ICT-pretreated patients, N (%)			All patients, N (%)		
	DFX GRAN N=54	DFX DT N=54	Overall N=108	DFX GRAN N=58	DFX DT N=58	Overall N=116	DFX GRAN N=112	DFX DT N=112	Overall N=224
Median age in years (range)	2.0 (2.0-13.0)	2.0 (2.0-13.0)	2.0 (2.0-13.0)	8.0 (4.0-10.0)	7.0 (5.0-10.0)	7.5 (4.0-10.0)	4.5 (2.0-15.0)	5.0 (2.0-16.0)	5.0 (2.0-16.0)
Sex									
Male	29 (53.7)	29 (53.7)	58 (53.7)	27 (46.6)	29 (50.0)	56 (48.3)	56 (50.0)	58 (51.8)	114 (50.9)
Female	25 (46.3)	25 (46.3)	50 (46.3)	31 (53.4)	29 (50.0)	60 (51.7)	56 (50.0)	54 (48.2)	110 (49.1)
Race									
White	25 (46.3)	25 (46.3)	50 (46.3)	27(46.6)	32 (55.2)	59(50.9)	52 (46.4)	57 (50.9)	109 (48.7)
Asian	19 (35.2)	19 (35.2)	38 (35.2)	25 (43.1)	19 (32.8)	44 (37.9)	44 (39.3)	38 (33.9)	82 (36.6)
Black/African American	4 (7.4)	5 (9.3)	9 (8.3)	4(6.9)	6(10.3)	10(8.6)	8 (7.1)	11 (9.8)	19 (8.5)
Other	6 (11.1)	4 (7.4)	10 (9.3)	2(3.4)	1(1.7)	3(2.6)	8 (7.1)	5 (4.5)	13 (5.8)
Missing	0	1 (1.9)	1 (0.9)	-	-	-	0	1 (0.9)	1 (0.4)
Median time since diagnosis in years (range)	1.9 (0.0-13.0)	2.1 (0.4-8.1)	2.0 (0.0-13.0)	5.86 (1.4-13.9)	6.46 (0.1-16.0)	6.26 (0.1-16.0)	3.6 (0.0-13.9)	3.6 (0.1-16.0)	3.6 (0.0-16.0)
Underlying condition for transfusion, N (%)									
β-thalassemia major	29 (53.7)	36 (66.7)	65 (60.2)	38 (65.5)	39 (67.2)	77 (66.4)	67 (59.8)	75 (67.0)	142 (63.4)
Sickle cell	8 (14.8)	6 (11.1)	14 (13.0)	4 (6.9)	5 (8.6)	9 (7.8)	12 (10.7)	11 (9.8)	23 (10.3)
Hemoglobin E-disorder	3 (5.6)	4 (7.4)	7 (6.5)	9 (15.5)	8 (13.8)	17 (4.7)	12 (10.7)	12 (10.7)	24 (10.7)
Hemolytic anemia	2 (3.7)	2 (3.7)	4 (3.7)	1 (1.7)	1 (1.7)	2 (1.7)	3 (2.7)	3 (2.7)	6 (2.7)
β-thalassemia intermedia	1 (1.9)	2 (3.7)	3 (2.8)	0	1 (1.7)	1 (0.9)	1 (0.9)	3 (2.7)	4 (1.8)
Diamond-Blackfan anemia*	1 (1.9)	1 (1.9)	2 (1.8)	1 (1.7)	1 (1.7)	2 (1.7)	2 (1.8)	2 (1.8)	4 (1.8)
Fanconi's anemia	1 (1.9)	0	1 (0.9)	-	-	-	1 (0.9)	0	1 (0.4)
Sideroblastic anemia	1 (1.9)	0	0	-	-	-	1 (0.9)	0	1 (0.4)
Other	8 (14.8)	3 (5.6)	11 (10.2)	5 (8.6)	3 (5.2)	8 (6.9)	13 (11.6)	6 (5.4)	19 (8.5)
Prior ICT	2 (3.7)	0	2 (1.9)	57 (98.3)	58 (100.0)	115 (99.1)	59 (52.7)	58 (51.8)	117 (52.2)
DFX prior to study									
Yes	2 (3.7)	0	2 (1.9)	41 (70.7)	38 (65.5)	79 (68.1)	43 (38.4)	38 (33.9)	81 (36.2)
No	52 (96.3)	54 (100.0)	106 (98.1)	17 (29.3)	20 (34.5)	37 (31.9)	16 (14.3)	20 (17.9)	36 (16.1)
Missing	-	-	-	-	-	-	53 (47.3)	54 (48.2)	107 (47.8)
Median time since last ICT† in years (range)	6.81 (4.5-9.1)	0	6.81 (4.5-9.1)	0.73 (0.0-8.6)	1.31 (0.0-9.5)	0.91 (0.0-9.5)	0.8 (0.0-9.5)	1.3 (0.0-9.5)	0.9 (0.0-9.5)

*Including red cell aplasia; †N values: 48, 51, and 99 for deferasirox granules, deferasirox DT, and overall, respectively. DFX: deferasirox; DT: dispersible tablet; GRAN: granules; ICT: iron chelation therapy.

populations after end of treatment (EOT)-core. After EOT-core, mean (SD) changes from baseline in SF with deferasirox granules and deferasirox DT, respectively, were 317.0 (834.8) ng/mL and 305.8 (1,026.8) ng/mL in the ICT-naive patients (N=46 and N=47, respectively), 215.7 (936.7) ng/mL and 207.7 (1,084.7) ng/mL in the ICT-pretreated patients (N=50 and N=52, respectively) and 264.3 (886.1) ng/mL and 254.2 (1,053.4) ng/mL in the overall population (N=96 and N=99, respectively).

PRO/ObsRO questionnaires

The mSICT questionnaire domain scores by both ObsRO and PRO for the overall population are presented in *Online Supplementary Table S3*. Higher scores for adherence and satisfaction/preference indicate worse adherence and satisfaction/preference, while higher scores for concerns indicate fewer concerns. Mean (SD) scores for adherence and satisfaction/preference at EOT-core were 6.8 (2.6) by ObsRO caregiver and 3.1 (0.9) by PRO respectively with deferasirox granules and 7.5 (2.5) by ObsRO and 4.8 (2.2) by PRO respectively with deferasirox DT, indicating better adherence and satisfaction/preference with granules *versus* DT. Mean scores for concerns with deferasirox granules and deferasirox DT at EOT-core were 4.6 (0.8) and 4.0 (1.2) by ObsRO caregiver, respectively, indicating fewer concerns with granules *versus* DT (*Online Supplementary Table S3*). The palatability questionnaire has a minimum score of 0 and a maximum score of 11, with a higher score represent-

ing better palatability. Mean palatability scores by ObsRO with deferasirox granules and deferasirox DT at EOT-core were 10.9 (1.0) and 9.0 (3.1), respectively, indicating better palatability with granules *versus* DT (*Online Supplementary Table S4*). Supportive analysis, conducted to check the robustness of the results obtained from the mSICT and palatability ObsRO questionnaires, concurs with these results (using data from the overall patient population; Figure 4 and ICT-naive and ICT-pretreated data in *Online Supplementary Figures S3* and *S4*).

Table 2. Exposure to deferasirox.

Exposure variable	ICT-naive patients, N (%)		ICT-pretreated patients, N (%)		All patients, N (%)	
	DFX GRAN N=52	DFX DT N=54	DFX GRAN N=58	DFX DT N=57	DFX GRAN N=110	DFX DT N=111
Average planned dose, mg/kg/day						
Mean (SD)	16.7 (3.22)	22.8 (5.39)	19.5 (4.61)	27.7 (7.1)	18.2 (4.2)	25.3 (6.8)
Median (range)	15.7 (10.0-23.5)	21.4 (8.6-35.2)	18.6 (10.5-28.0)	28.2 (10.0-40.0)	17.8 (10.0-28.0)	23.6 (8.6-40.0)
Average planned dose category, mg/kg/day						
<15 DT/<10.5 granule	1 (1.9)	3 (5.6)	0	2 (3.5)	1 (0.9)	5 (4.5)
15 to <25 DT/10.5 to <17.5 granule	32 (61.5)	37 (68.5)	18 (31.0)	19 (33.3)	50 (45.5)	56 (50.5)
25 to <35 DT/17.5 to <24.5 granule	19 (36.5)	13 (24.1)	30 (51.7)	26 (45.6)	49 (44.6)	39 (35.1)
≥35 DT/≥24.5 granule	0	1 (1.9)	10 (17.2)	10 (17.5)	10 (9.1)	11 (9.9)
Average actual dose, mg/kg/day						
Mean (SD)	16.7 (3.15)	22.9 (5.73)	19.1 (4.51)	27.2 (6.9)	18.0 (4.1)	25.1 (6.7)
Median (range)	16.2 (10.5-24.4)	22.5 (7.7-37.8)	18.7 (10.2-28.8)	27.9 (8.7-39.4)	17.5 (10.2-28.8)	24.0 (7.7-39.4)
Average actual dose category, mg/kg/day						
<15 DT/<10.5 granule	0	3 (5.6)	1 (1.7)	4 (7.0)	1 (0.9)	7 (6.3)
15 to <25 DT/10.5 to <17.5 granule	34 (65.4)	37 (68.5)	21 (36.2)	18 (31.6)	55 (50.0)	55 (49.6)
25 to <35 DT/17.5 to <24.5 granule	18 (34.6)	12 (22.2)	26 (44.8)	28 (49.1)	44 (40.0)	40 (36.0)
≥35 DT/≥24.5 granule	0	2 (3.7)	10 (17.2)	7 (12.3)	10 (9.1)	9 (8.1)
Cumulative actual dose, mg/kg						
Mean (SD)	104.1 (75.71)	142.0 (149.50)	159.6 (150.90)	220.6 (221.16)	133.4 (123.9)	182.3 (192.9)
Median (range)	83.2 (12.4-351.5)	90.3 (17.9-886.1)	97.9 (10.2-698.8)	178.9 (20.6-1,495.3)	93.0 (10.2-698.8)	129.8 (17.9-1,495.3)
Percentage of planned dose taken	75.8 (19.91)	71.7 (23.46)	65.9 (24.03)	64.1 (19.76)	70.6 (22.6)	67.8 (21.9)
Mean (SD)	72.0	63.9	62.3	60.1	67.2	62.6
Median (range)	(40.6-114.9)	(35.3-123.8)	(27.1-116.6)	(23.0-106.1)	(27.1-116.6)	(23.0-123.8)
Days on treatment						
Mean (SD)	332.4 (45.02)	303.6 (84.9)	308.3 (80.0)	290.8 (95.5)	319.7(66.6)	297.0 (90.3)
Median (range)	337.0 (27-370)	336.5 (14-378)	336 (8-366)	336 (7-355)	337.0 (8-370)	336.0 (7-378)
Exposure categories						
<4 weeks	1 (1.9)	1 (1.9)	2 (3.4)	3 (5.3)	3 (2.7)	4 (3.6)
4 weeks to <12 weeks	0	2 (3.7)	0	1 (1.8)	0	3 (2.7)
12 weeks to <20 weeks	0	2 (3.7)	3 (5.2)	2 (3.5)	3 (2.7)	4 (3.6)
20 weeks to <28 weeks	0	2 (3.7)	1 (1.7)	2 (3.5)	1 (0.9)	4 (3.6)
28 weeks to <36 weeks	0	1 (1.9)	1 (1.7)	4 (7.0)	1 (0.9)	5 (4.5)
36 weeks to <44 weeks	2 (3.8)	3 (5.6)	1 (1.7)	1 (1.8)	3 (2.7)	4 (3.6)
≥44 weeks	49 (94.2)	43 (79.6)	50 (86.2)	44 (77.2)	99 (90.0)	87 (78.4)
Total patient years						
Mean (SD)	0.9 (0.12)	0.8 (0.23)	0.8 (0.22)	0.8 (0.26)	0.9 (0.2)	0.8 (0.2)
Median (range)	0.9 (0.1-1.0)	0.9 (0.0-1.0)	0.9 (0.0-1.0)	0.9 (0.0-1.0)	0.9 (0.0-1.0)	0.9 (0.0-1.0)

DFX: deferasirox; DT: dispersible tablet; GRAN: granules; ICT: iron chelation therapy; SD: standard deviation.

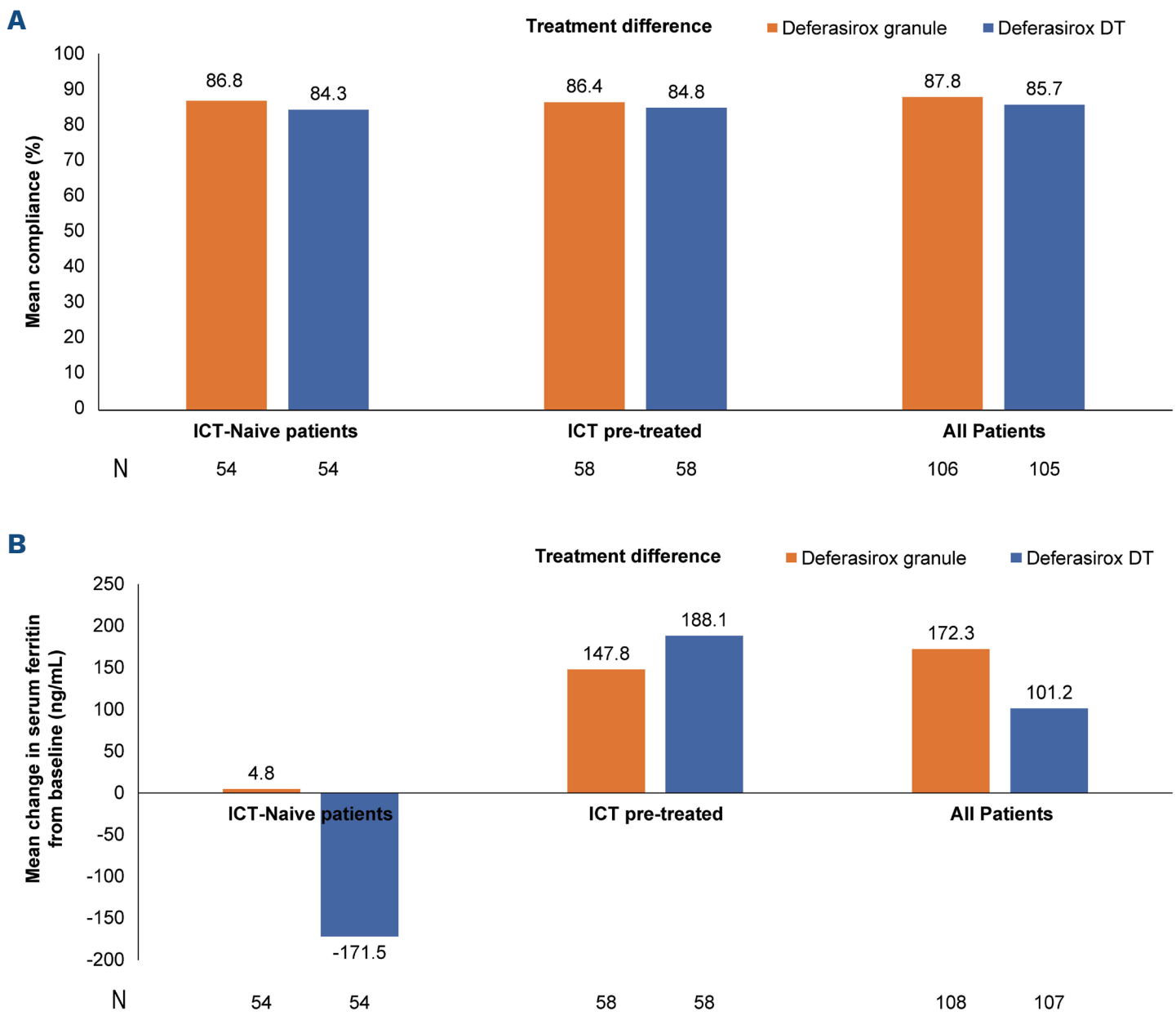

Figure 2. Co-primary endpoints for iron chelation therapy-naive, iron chelation therapy-pretreated patients and overall patient populations at 24 weeks. (A) Compliance. (B) Change from baseline in serum ferritin*. *Based on ANCOVA analysis showing least squares mean change in serum ferritin from baseline to 24 weeks. DT: dispersible tablet; ICT: iron chelation therapy.

For the compliance ObsRO diary, the weekly dose violation rate indicated overall lower mean weekly violation rates from week 1 to week 48 in the defarasirox DT arm compared with defarasirox granules (mean weekly dose violation rate range for weeks 1 to 48, 7.8 to 18.8 and 13.7 to 27.8, respectively). For the compliance PRO diary, the results should be interpreted with caution due to the low number of patients completing the questionnaire (*Online Supplementary Figure S5*).

Pharmacokinetic analysis

As there were fewer than 12 patients with an evaluable PK profile, no PK parameters were derived. Geometric means (CV% geo-mean) of dose-adjusted pre-dose data for deferasirox granules and deferasirox DT, respectively, were 1.4 μmol/L (235.4%) and 2.9 μmol/L (369.5%) at week 1, 17.7 μmol/L (106.5%) and 16.9 μmol/L (148.2%) at week 25, and 19.8 μmol/L (119.1%) and 28.2 μmol/L (141.7%) at week 45 (*Online Supplementary Figure S6*).

Pre-dose PK analysis was used to support the assessment of compliance. Predicted steady-state pre-dose concentrations from a power model (using the log-transformed weight-adjusted dose and treatment group as fixed effects and patient as a random effect) were used to derive differences between predicted and observed concentration values. The mean differences between the deferasirox granules and DT groups were comparable (-6.9 and -9.3, respectively). However, the variance of the differences in the deferasirox granules and DT groups were 700.6 and 1,370.9, respectively. Higher compliance is expected to lead to lower variability of differences between the predicted and observed concentrations; as such, the higher variance of difference in deferasirox DT arm than in deferasirox granules arm suggested better compliance in deferasirox granules arm. At low pre-dose concentrations, SF change from baseline increased over time and at high pre-dose concentrations, SF change from baseline decreased over time. Increases in pre-dose concentrations and time were associated with an increase in serum creatinine, urinary protein/creatinine ratio (UPCR) and a decrease in creatinine clearance from baseline.

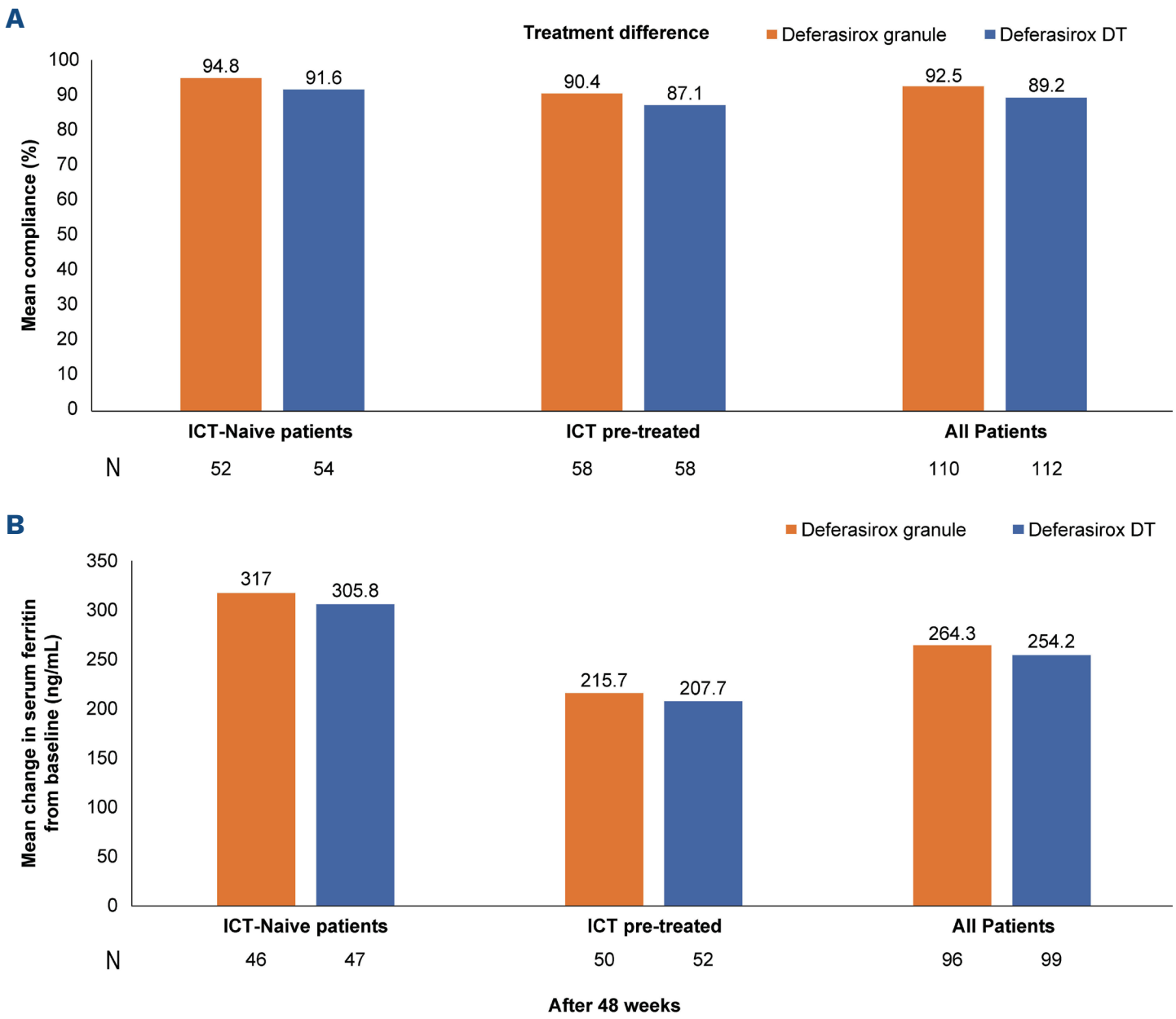

Figure 3. Summary of overall compliance and absolute change from baseline in serum ferritin. (A) Mean compliance after 48 weeks. (B) Mean change in serum ferritin from baseline after 48 weeks*. *Based on observed mean change in serum ferritin from baseline to 48 weeks. DT: dispersible tablet; ICT: iron chelation therapy.

Safety

An overview of safety for the overall patient population is shown in Table 3. The incidence of overall AE was similar in the two treatment groups (97.3% in the deferasirox DT group *vs*. 90.9% in the deferasirox granules group). The most commonly (≥ 20%) reported AE (by PT) in either of the treatment groups (in deferasirox DT group or the deferasirox granules group respectively) in the core phase were: upper respiratory tract infection (29.7% *vs*. 28.2%), pyrexia (23.4% *vs*. 26.4%), and urine protein/creatinine ratio increased (34.2% *vs*. 24.5%). The number of patients who had experienced AE suspected to be study drug related were similar in both treatment groups (57.7% and 52.7%) in the core phase. All AE suspected to be study drug-related were reported in <10% of the patients (in either of the treatment groups) with the exception of urine protein/creatinine ratio increased (27.9% in deferasirox DT group *vs*. 20.0% in deferasirox granules group) and ALT increased (7.2% in deferasirox DT group *vs*. 10.9% in deferasirox granules group) in the core phase. Overall, the incidence of SAE (regardless of study drug relationship) was similar in both treatment groups (20.7% *vs*. 24.5%) in the core phase. All SAE were reported in either one or two patients, with the exception of pyrexia (3.6% in both treatment groups), sickle cell anemia with crisis (4.5% *vs*. 2.7%), pneumonia (2.7% *vs*. 0.9%) and bronchitis (2.7% *vs*. 0) in the deferasirox DT and the deferasirox granules groups, respectively. No deaths were reported with either of the two treatments (Table 4).

In ICT-naive patients, the overall incidence of AE in the granules and DT groups was 90.4% and 100%, respectively. The most commonly reported AE in the deferasirox granules and deferasirox DT groups, respectively, were pyrexia (28.8% and 20.4%), upper respiratory tract infection (32.7% and 25.9%), and UPCR increased (21.2% and 24.1%). The profile was similar across treatment groups, as no AE were observed with a difference of >10%.

In the overall patient population, 32.7% and 41.4% of patients in the deferasirox granules and DT groups, respectively, experienced GI disorder AE. Vomiting (deferasirox granules, 8.2%; deferasirox DT, 13.5%) and diarrhea (deferasirox granules, 8.2%; deferasirox DT, 12.6%) were the most common GI AE in the

overall patient population (Table 4). In the ICT-naive patients, 28.8% and 35.2% of patients in the deferasirox granules and DT groups, respectively, experienced GI disorder AE. Diarrhea (deferasirox granules, 5.8%; deferasirox DT, 11.1%), abdominal pain (deferasirox granules, 9.6%; deferasirox DT, 1.9%), and vomiting (deferasirox granules, 7.7%; deferasirox DT, 7.4%) were the most common GI AE in the ICT-naive patients.

The incidence of AE leading to study drug discontinuation, regardless of study drug relationship, was low and similar in both treatment groups in the overall patient population (deferasirox granules, 4.5%; deferasirox DT, 7.2%) (*Online Supplementary Table S5*). In ICT-naive patients, the incidence of AE leading to study drug discontinuation, regardless of study drug relationship, was low in both treatment groups (deferasirox granules, 3.8%; deferasirox DT, 7.4%). The AE leading to study drug discontinuation were upper GI hemorrhage and transaminases increases in the deferasirox granules group and vomiting, blood creatinine increases, conjugated bilirubin increases, and proteinuria in the deferasirox DT group. Details of safety are covered in *Online Supplementary Tables S5-S9*.

Discussion

CALYPSO is a randomized, open-label, phase II study comparing the compliance and clinical benefit of two different deferasirox formulations (granules and DT) in pediatric patients with transfusion-dependent anemia requiring chelation therapy because of transfusional iron overload. The study did not meet its primary objective. No statistically significant difference was observed in compliance and SF change from baseline between granules and DT after 24 weeks. There was no improved compliance and clinical benefit in terms of changes in SF over time with granules.

This study was designed to show a difference of 10% between the two treatment groups and given the high compliance rate observed in the deferasirox DT group (84.3%), this objective was challenging to achieve. The ICT-naive patient population included mostly very young children (median age 2 years) who had limited capacity to decide treatment administration and required parental assistance. It has been previously shown that compliance with ICT in thalassemia patients is highest in children, followed by adolescents and adults aged 35 years and older. Thus, the high compliance in children most likely reflects parental adherence.[16] A similar observation was made in the overall patient population, which also included a young population (median age 5 years). Increases in SF were observed after 24 weeks and 48 weeks; the mean SF levels were found to be slightly increased during the core phase (i.e., approximately 1 year) and were similar between the two treatment arms at the end of the treatment core phase. However, a consistent decrease in mean SF values was observed with continuous deferasirox treatment beyond the core phase and during the extension phase. Earlier studies have reported a similar pattern of slight increase or maintenance of SF levels at 24 weeks with an

Table 3. Incidence of adverse events.

Category	ICT-naive patients, N (%)				ICT-pretreated patients, N (%)				All patients, N (%)			
	DFX GRAN N=52		DFX DT N=54		DFX GRAN N=58		DFX DT N=57		DFX GRAN N=110		DFX DT N=111	
	All AE	Severe AE	All AE	Severe AE	All AE	Severe AE	All AE	Severe AE	All AE	Severe AE	All AE	Severe AE
AE	47 (90.4)	18 (34.6)	54 (100)	14 (25.9)	53 (91.4)	15 (25.9)	54 (94.7)	20 (35.1)	100 (90.9)	33 (30.0)	108 (97.3)	34 (30.6)
Suspected AE	25 (48.1)	7 (13.5)	22 (40.7)	3 (5.6)	33 (56.9)	8 (13.8)	42 (73.7)	11 (19.3)	58 (52.7)	15 (13.6)	64 (57.7)	14 (12.6)
SAE	14 (26.9)	9 (17.3)	13 (24.1)	10 (18.5)	13 (22.4)	7 (12.1)	10 (17.5)	8 (14.0)	27 (24.5)	16 (14.5)	23 (20.7)	18 (16.2)
Suspected SAE	1 (1.9)	1 (1.9)	0	0	2 (3.4)	2 (3.4)	2 (3.5)	2 (3.5)	3 (2.7)	3 (2.7)	2 (1.8)	2 (1.8)
AE leading to study drug discontinuation	2 (3.8)	2 (3.8)	4 (7.4)	1 (1.9)	3 (5.2)	1 (1.7)	4 (7.0)	4 (7.0)	5 (4.5)	3 (2.7)	8 (7.2)	5 (4.5)
AE requiring dose adjustment and/or interruption	24 (46.2)	7 (13.5)	32 (59.3)	8 (14.8)	29 (50.0)	8 (13.8)	37 (64.9)	15 (26.3)	53 (48.2)	15 (13.6)	69 (62.2)	23 (20.7)
AE requiring additional therapy	39 (75.0)	11 (21.2)	44 (81.5)	11 (20.4)	43 (74.1)	9 (15.5)	41 (71.9)	10 (17.5)	82 (74.5)	20 (18.2)	85 (76.6)	21 (18.9)
AE of special interest	30 (57.7)	12 (23.1)	27 (50.0)	5 (9.3)	35 (60.3)	9 (15.5)	41 (71.9)	13 (22.8)	65 (59.1)	21 (19.1)	68 (61.3)	18 (16.2)

Patients with multiple events in the same category were counted only once in that category. Patients with events in more than 1 category were counted once in each of those categories. AE: adverse event; DFX: deferasirox; DT: dispersible tablet; GRAN: granules; ICT: iron chelation therapy; SAE: serious adverse event.

Table 4. Overall incidence of common (>10%) adverse events.

	ICT-naive patients, N (%)				ICT-pretreated, N (%)				All patients, N (%)			
	DFX GRAN N=52		DFX DT N=54		DFX GRAN N=58		DFX DT N=57		DFX GRAN N=110		DFX DT N=111	
	All AE	Severe AE	All AE	Severe AE	All AE	Severe AE	All AE	Severe AE	All AE	Severe AE	All AE	Severe AE
UPCR increased	11 (21.2)	2 (3.8)	13 (24.1)	1 (1.9)	16 (27.6)	2 (3.4)	25 (43.9)	3 (5.3)	27 (24.5)	4 (3.6)	38 (34.2)	4 (3.6)
Upper respiratory tract infection	17 (32.7)	0	14 (25.9)	0	14 (24.1)	0	19 (33.3)	0	31 (28.2)	0	33 (29.7)	0
Pyrexia	15 (28.8)	2 (3.8)	11 (20.4)	0	14 (24.1)	2 (3.4)	15 (26.3)	2 (3.5)	29 (26.4)	4 (3.6)	26 (23.4)	2 (1.8)
ALT increased	7 (13.5)	5 (9.6)	5 (9.3)	0	13 (22.4)	3 (5.2)	10 (17.5)	7 (12.3)	20 (18.2)	8 (7.3)	15 (13.5)	7 (6.3)
Bilirubin conjugated increased	5 (9.6)	0	5 (9.3)	0	7 (12.1)	0	11 (19.3)	0	12 (10.9)	0	16 (14.4)	0
Vomiting	4 (7.7)	0	4 (7.4)	0	5 (8.6)	0	11 (19.3)	0	9 (8.2)	0	15 (13.5)	0
Cough	6 (11.5)	0	5 (9.3)	0	8 (13.8)	0	7 (12.3)	0	14 (12.7)	0	12 (10.8)	0
Diarrhea	3 (5.8)	0	6 (11.1)	0	6 (10.3)	0	8 (14.0)	0	9 (8.2)	0	14 (12.6)	0
Nasopharyngitis	6 (11.5)	0	7 (13.0)	1 (1.9)	5 (8.6)	0	6 (10.5)	0	11 (10.0)	0	13 (11.7)	1 (0.9)
AST increased	5 (9.6)	1 (1.9)	3 (5.6)	0	7 (12.1)	2 (3.4)	8 (14.0)	1 (1.8)	12 (10.9)	3 (2.7)	11 (9.9)	1 (0.9)
Abdominal pain	5 (9.6)	0	1 (1.9)	0	7 (12.1)	0	3 (5.3)	0	12 (10.9)	0	4 (3.6)	0
Pharyngitis	5 (9.6)	1 (1.9)	1 (1.9)	0	6 (10.3)	0	2 (3.5)	0	11 (10.0)	1 (0.9)	3 (2.7)	0

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DFX: deferasirox; DT: dispersible tablet; GRAN: granules; ICT: iron chelation therapy; UPCR: urinary protein/creatinine ratio.

initial dose of deferasirox DT 20 mg/kg; this was attributed to the disproportionately low initial doses given to regularly transfused patients with moderate iron overload.[17,18]

The PRO analyses were performed using PRO/ObsRO scores from the mSICT questionnaire and palatability scores. The study results indicated that the adherence and satisfaction/preference scores were numerically lower (indicates better) and the concerns score higher (indicates fewer) with granules *versus* DT. The palatability scores were numerically higher (indicates better) with granules *versus* DT. These results were further confirmed by supportive analysis. However, due to the small number of patients old enough/able to complete PRO questionnaires (N=41, 18.3%), PRO data should be interpreted with caution. Despite slight differences between deferasirox granules and DT arms in the ObsRO/PRO scores for adherence, satisfaction/preference (ObsRO only), concerns, and palatability, the overall scores for both formulations were closer to the lower score range for adherence and satisfaction/preference and the higher score range for concerns and palatability. This indicates overall good adherence, satisfaction/preference, fewer concerns, and good palatability with both deferasirox formulations.

A similar, yet limited, observation was reported in a retrospective study by Higashino *et al.* (5 adult patients).[19] Patient satisfaction was higher for deferasirox granules than for deferasirox DT considering all four assessed items (for handiness: 85±6 *vs*. 40±17 mm, P=0.001; ease of administration: 64±28 *vs*. 27±12 mm, P=0.037; administration timing: 90±6 *vs*. 21±17 mm, P<0.001; and taste: 66±19 *vs*. 39±10 mm, P=0.033, using a 100-mm visual analog scale for all 4 items).[19] In the ECLIPSE study, the PRO analyses indicated that overall satisfaction scores were higher with deferasirox FCT compared with deferasirox DT.[20] The FCT formulation, similar to the granule formulation, was developed to improve palatability, tolerability, and patient compliance.

The pre-dose PK exposure analysis demonstrated a lower variance of the differences between predicted and observed concentration values in the deferasirox granules group compared with the deferasirox DT group, indicating better compliance with granules.

In the present study, a higher proportion of patients in the overall patient population in the deferasirox DT group experienced GI AE compared with the deferasirox granules group (41.4% *vs*. 32.7%). As deferasirox granules can be taken with a light meal, and also lack the excipients lac-

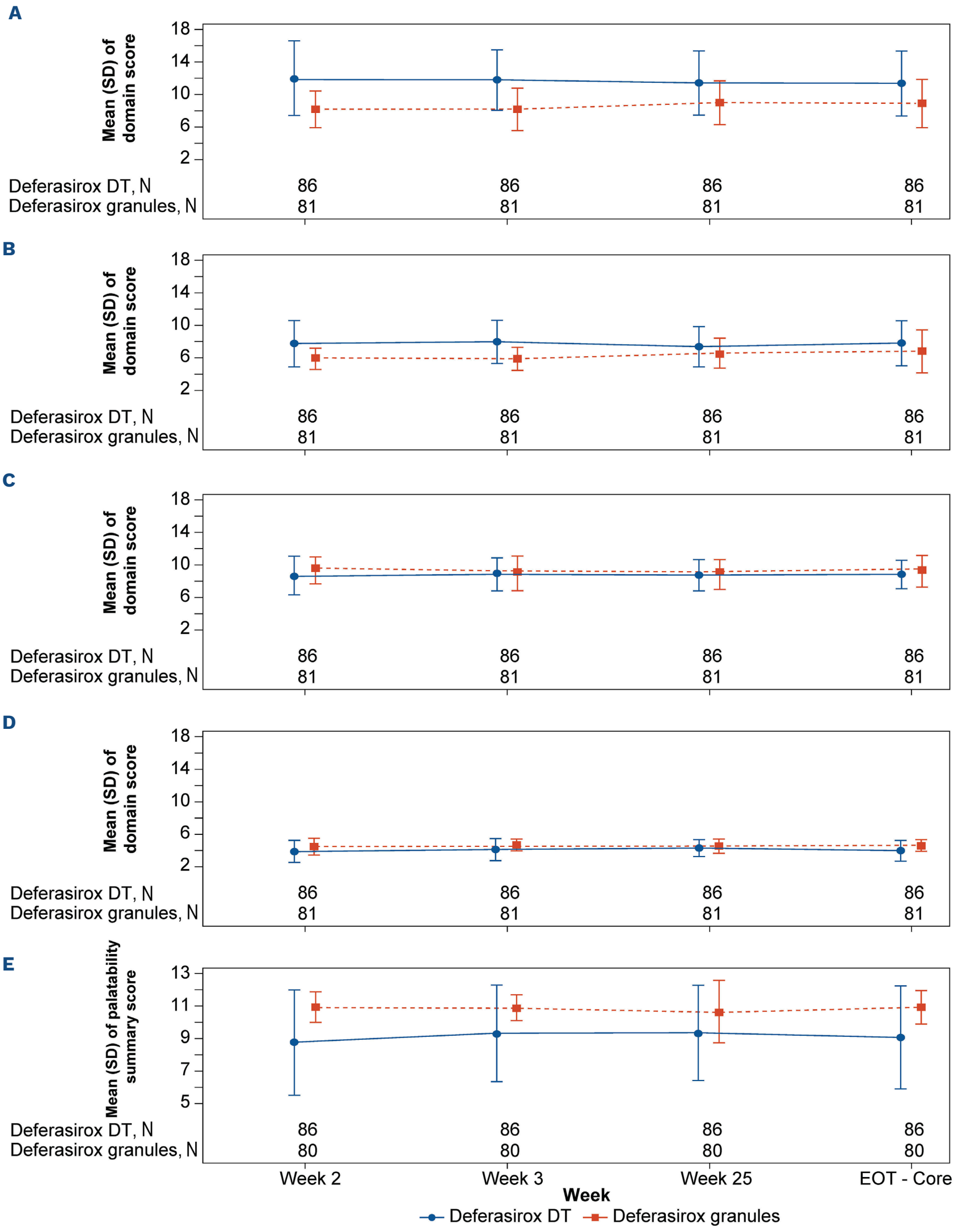

Figure 4. PRO/ObsRO questionnaires (all patients). (A) Modified SICT ObsRO (child adherence). (B) Modified SICT ObsRO (caregiver adherence). (C) Modified SICT ObsRO (child concerns). (D) Modified SICT ObsRO (caregiver concerns). (E) Palatability ObsRO. DT: dispersible tablet; ObsRO: observer-reported outcome; PRO: patient-reported outcome; SICT: satisfaction iron chelation therapy.

tose and sodium lauryl sulfate, both found in the original DT formulation and possibly implicated in GI AE, it was expected that deferasirox granules would show improved GI tolerability. The present study results suggest that the GI tolerability profile may be improved with granules compared with DT, which could be because of the change in excipients and/or the ability to take the medicine with a light meal. However, long-term study data are required to confirm this observation.

One patient on deferasirox DT experienced acquired Fanconi syndrome, leading to discontinuation of the drug. There are earlier reports of development of this AE in deferasirox-treated patients, with cessation of deferasirox leading to prompt recovery.[21,22] Overall, the safety profile was comparable between deferasirox granules and deferasirox DT and consistent with previous studies; no new safety signals were observed.

In conclusion, the study did not meet its primary objective. In ICT-naive patients, mean compliance and change from baseline in SF with deferasirox granules and DT formulations were not significantly different. No new safety signals were identified in this study and the study treatments were well tolerated.

Disclosures

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Contributions

All authors met the International Council of Medical Journal Editors' criteria for authorship and all those who met those criteria are listed as authors. All authors contributed to the conceptualization, design, acquisition, analysis and interpretation of data, and development of this manuscript. All authors approved the final manuscript for submission. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Data-sharing statement

Novartis is committed to sharing with qualified external researchers, access to patient-level data, and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with the applicable laws and regulations. The availability of trial data is according to the criteria and process described on www.clinicalstudydatarequest.com.

References

1. Fernandes JL, Fabron A, Jr., Verissimo M. Early cardiac iron overload in children with transfusion-dependent anemias. Haematologica. 2009;94(12):1776-1777.
2. Gordan R, Wongjaikam S, Gwathmey JK, Chattipakorn N, Chattipakorn SC, Xie LH. Involvement of cytosolic and mitochondrial iron in iron overload cardiomyopathy: an update. Heart Fail Rev. 2018;23(5):801-816.
3. Saliba AN, Harb AR, Taher AT. Iron chelation therapy in transfusion-dependent thalassemia patients: current strategies and future directions. J Blood Med. 2015;6:197-209.
4. Vichinsky E, Butensky E, Fung E, et al. Comparison of organ dysfunction in transfused patients with SCD or beta thalassemia. Am J Hematol. 2005;80(1):70-74.
5. Novartis Pharma AG. Exjade® (deferasirox) [Prescribing information]. U.S. Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021882s006lbl.pdf. Revised April 2009. Accessed August 2023.
6. Aydinok Y, Unal S, Oymak Y, et al. Observational study comparing long-term safety and efficacy of Deferasirox with Desferrioxamine therapy in chelation-naive children with transfusional iron overload. Eur J Haematol. 2012;88(5):431-438.
7. Vichinsky E, El-Beshlawy A, Al Zoebie A, et al. Long-term safety and efficacy of deferasirox in young pediatric patients with transfusional hemosiderosis: results from a 5-year observational study (ENTRUST). Pediatr Blood Cancer. 2017;64(9):e26507.
8. Osborne RH, De Abreu Lourenco R, Dalton A, et al. Quality of life related to oral versus subcutaneous iron chelation: a time trade-off study. Value Health. 2007;10(6):451-456.
9. Delea TE, Sofrygin O, Thomas SK, Baladi JF, Phatak PD, Coates TD. Cost effectiveness of once-daily oral chelation therapy with deferasirox versus infusional deferoxamine in transfusion-dependent thalassaemia patients: US healthcare system perspective. Pharmacoeconomics. 2007;25(4):329-342.
10. Haghpanah S, Zarei T, Zahedi Z, Karimi M. Compliance and

satisfaction with deferasirox (Exjade(R)) compared with deferoxamine in patients with transfusion-dependent beta-thalassemia. Hematology. 2014;19(4):187-191.
11. Vichinsky E. Clinical application of deferasirox: practical patient management. Am J Hematol. 2008;83(5):398-402.
12. Gabutti V, Piga A. Results of long-term iron-chelating therapy. Acta Haematol. 1996;95(1):26-36.
13. Delea TE, Edelsberg J, Sofrygin O, et al. Consequences and costs of noncompliance with iron chelation therapy in patients with transfusion-dependent thalassemia: a literature review. Transfusion. 2007;47(10):1919-1929.
14. Modell B, Khan M, Darlison M. Survival in beta-thalassaemia major in the UK: data from the UK Thalassaemia Register. Lancet. 2000;355(9220):2051-2052.
15. Novartis Pharmaceuticals Corporation. JADENU® (deferasirox) [Prescribing Information]. U.S. Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/207968s009lbl.pdf. Revised July 2020. Accessed August 2023.
16. Trachtenberg F, Vichinsky E, Haines D, et al. Iron chelation adherence to deferoxamine and deferasirox in thalassemia. Am J Hematol. 2011;86(5):433-436.
17. Cappellini MD, Cohen A, Piga A, et al. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with beta-thalassemia. Blood. 2006;107(9):3455-3462.
18. Taher A, El-Beshlawy A, Elalfy MS, et al. Efficacy and safety of deferasirox, an oral iron chelator, in heavily iron-overloaded patients with beta-thalassaemia: the ESCALATOR study. Eur J Haematol. 2009;82(6):458-465.
19. Higashino S, Yasu T, Momo K, Kuroda S. Effects of formulation changes for deferasirox from dispersible tablets to granules in patients with red blood cell transfusion-induced iron overload. Am J Ther. 2019;26(6):e728-e730.
20. Taher AT, Origa R, Perrotta S, et al. New film-coated tablet formulation of deferasirox is well tolerated in patients with thalassemia or lower-risk MDS: Results of the randomized, phase II ECLIPSE study. Am J Hematol. 2017;92(5):420-428.
21. Chuang GT, Tsai IJ, Tsau YK, Lu MY. Transfusion-dependent thalassaemic patients with renal Fanconi syndrome due to deferasirox use. Nephrology (Carlton). 2015;20(12):931-935.
22. Yacobovich J, Stark P, Barzilai-Birenbaum S, et al. Acquired proximal renal tubular dysfunction in beta-thalassemia patients treated with deferasirox. J Pediatr Hematol Oncol. 2010;32(7):564-567.