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

Ali T. Taher,[1] Yasser Wali,[2] Maria Cecilia Cruz,[3] Pimlak Charoenkwan,[4] Yesim Aydinok,[5] Olena Werner,[6] Sameera Govindaraju,[7] Fabian Romen[6] and Vip Viprakasit[8]

[1]American University of Beirut Medical Center, Beirut, Lebanon; [2]Sultan Qaboos University Hospital, Muscat, Oman; [3]Philippine Children's Medical Center, Quezon City, Republic of the Philippines; [4]Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; [5]Ege University, Faculty of Medicine, Izmir, Turkey; [6]Novartis Pharma AG, Basel, Switzerland; [7]Novartis Healthcare Pvt Ltd, Hyderabad, India and [8]Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

Correspondence: A.T. Taher
ataher@aub.edu.lb

Received: March 30, 2023.
Accepted: October 13, 2023.
Early view: October 19, 2023.

https://doi.org/10.3324/haematol.2023.283133

Supplementary Materials

Methods

Exclusion criteria

Creatinine clearance below the contraindication limit according to the local label; serum creatinine >1.5 x upper limit of normal (ULN); liver disease with severity of Child-Pugh class B or C; urinary protein/creatinine ratio (UPCR) >0.5 mg/mg; alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >3.0 x ULN; direct (conjugated) bilirubin >2 x ULN; and impaired gastrointestinal (GI) function or GI disease that might significantly alter the absorption of oral deferasirox.

Randomization procedure

All patients who fulfilled all inclusion/exclusion criteria were randomized via Interactive Response Technology (IRT) to one of the treatment arms. Randomization was stratified by age groups (2 to <10 years, 10 to <18 years) and by prior iron chelation therapy (ICT; Yes/No). The randomization numbers were generated using the following procedures to ensure that treatment assignment was unbiased and concealed from patients and investigator staff. A patient randomization list was produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers were linked to the different treatment arms, which in turn were linked to medication numbers. A separate medication randomization list was produced by or under the responsibility of Novartis Drug Supply Management using a validated

system that automates the random assignment of medication numbers to medication packs containing each of the study treatments.

The investigator or his/her delegate logged on to the IRT and confirmed that the patient fulfilled all the inclusion/exclusion criteria. The IRT assigned a randomization number to the patient, which was used to link the patient to a treatment arm and specified a unique medication number for the first package of study treatment to be dispensed to the patient. The randomization number was not communicated to the caller.

During optional extension phase, all patients were provided with new deferasirox formulation (granules). No randomization was done. The randomization scheme for patients was reviewed and approved by a member of the Novartis Randomization Office.

Treatment blinding

This was an open-label study and patients, investigators, study site staff and sponsor had full knowledge of treatment allocation.

Treating the patient

Each patient was identified in the study by a Patient Number (Patient No.), that was assigned when the patient was first enrolled for screening and was retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient No. consisted of the Center Number (Center No., as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each

patient was numbered uniquely across the entire database. Upon signing the informed consent form, the patient was assigned to the next sequential Patient No.

Study drugs were to be dispensed to the patient by authorized site personnel only. The study medication packaging had a 2-part label. A unique medication number was printed on each part of this label which corresponded to one of the treatment arms. Responsible site personnel identified the study treatment packages to be dispensed to the patient by using the IRT and obtained the medication numbers. Site personnel added the patient numbers on the label. Immediately before dispensing the package to the patient, site personnel detached the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique Patient number.

Deferasirox dispersible tablet (DT) or granules were to be taken as follows:

- Patients randomized to deferasirox DT arm, were instructed to take the deferasirox DT every day on an empty stomach, at least 30 minutes before the next meal. The patient had to disperse the required number of deferasirox tablets in an appropriate amount of water, apple juice or orange juice. Gentle stirring was to be applied and continued until the tablets were fully disintegrated, which would take approximately 1 to 3 minutes. Immediately, after full disintegration of the tablets, the entire content of the glass was to be swallowed.
- Patients randomized to deferasirox granules, were instructed to take the granules by sprinkling the full dose on a soft food (e.g., yogurt, applesauce or warm porridge). The dose was to be immediately and completely consumed, and not stored for future use. The granules were to be taken once a day, preferably at the

same time each day, and might be taken on an empty stomach or with a light meal.

In ICT-naive patients, the starting dose was reduced by 50% when creatinine clearance at the start of the study was ≥40 mL/min and <60 mL/min (where locally applicable). The ICT–pre-treated patients needed to start their treatment at 50% of the pre-washout dose when creatinine clearance was ≥40 mL/min and <60 mL/min during at least one screening visit. For patients unable to tolerate the protocol-specified dosing schedule, dose reductions were permitted.

Assessments

Treatment compliance was evaluated by both direct and indirect methods. The stick pack/tablet count was performed by the investigator or study personnel every 4 weeks (weeks 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, and 45, and at end of treatment [EOT]) during the core phase. Assessment of compliance using stick pack/tablet counts was based on the actual count at the different time points, taking into account the amount of medication dispensed, returned, and reported as lost/wasted by the patient in the core phase. Pharmacokinetic blood samples were collected from all patients at the week 1, 3, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, and 45 visits as a part of direct assessment of treatment compliance (no pharmacokinetic samples were collected at the trial site in Egypt). Indirect methods included asking the patients how easy it is for them to take their prescribed medication, performing pill counts, collecting patient questionnaires, and assessing children's adherence by asking the help of a caregiver.

To assess the eligibility of a patient, a serum ferritin (SF) test was performed at screening visits 1 and 2 (in the absence of infection). The baseline SF value was

defined as the average of the two measurements obtained during the screening period. Thereafter, SF testing was performed at the week 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, and 45, and EOT visits to evaluate the clinical benefit related to improved compliance of the new formulation.

Patient satisfaction, palatability, and compliance were measured for both formulations using patient/observer-reported outcome (PRO/ObsRO) questionnaires. Three questionnaires were developed to evaluate both formulations: the modified Satisfaction with Iron Chelation Therapy (mSICT), a palatability questionnaire, and a compliance diary. For patients aged 10 to <18 years at enrollment, the PRO questionnaires were completed by the patients themselves. The questionnaires for patients aged 2 to <10 years were designed as observations made by caregivers such as the parent or legal guardian (ObsRO). Questionnaires had to be completed at visits 4 (week 2), 5 (week 3), 11 (week 25), and 777 (within 7 days of the last dose of treatment for those not continuing to the extension phase). The mSICT PRO questionnaire contained three domains (adherence, preference, and concerns). The ObsRO comprised two separate scales to capture the child's and caregiver's perspectives; these were further subdivided into three domains for the child, namely concerns, preference, and adherence, and two domains for the caregiver, namely concerns and adherence.

Safety was evaluated by monitoring and assessing adverse events (AE) and serious AE, with their severity and relationship to study drug, and pregnancies. The severity of AE was assessed in this trial as mild, moderate, severe, and life-threatening (corresponding to Common Terminology Criteria for Adverse Events [CTCAE] grades 1–4). CTCAE grade 5 (death) was not used in this study; nevertheless, information about deaths was collected though an EOT form during the treatment period.

Statistical Methods

Domain scores from the mSICT questionnaire and palatability summary scores were summarized using standard descriptive statistics by treatment arm, type of questionnaire (ObsRO questionnaire vs PRO questionnaire) and time point (weeks 2, 3, 25, and core EOT). Based on the compliance diary, a weekly average dose violation rate was calculated and summarized using descriptive statistics by treatment arm, type of questionnaire, and time. Supportive analyses to assess the robustness of the mSICT and palatability questionnaire for the ObsRO after imputing missing values using the multiple imputation method under the missing at random assumption were performed. Multiple imputation was not performed on PRO questionnaires due to the limited sample size. AE were summarized by presenting the number and percentage of patients having ≥1 AE.

Sample size calculation for the study

The sample size was estimated to demonstrate superiority of the deferasirox granule formulation and statistical significance for both co-primary endpoints in ICT-naive patients.

The assumptions made for this study were:

- For SF: An expected improvement with deferasirox granules over deferasirox DT in SF change from baseline to week 24 of treatment of −450 ng/mL with a standard deviation (SD) of 900 ng/mL based on results from study CICL670A0107 in pediatric patients treated with Exjade on ≥25 mg/kg/day at 24-weeks of treatment.
- For compliance using stick packs or tablets counts: An expected improvement with deferasirox granules over deferasirox DT in mean relative consumed tablet count of 10% with a SD equal to 17.625% based on the pooled analysis on pediatric patients (77) from Exjade studies (ICL670A2206; 39 patients, ICL670A2204; 24 patients and ICL670A2214; 14 patients).

The sample size for the ICT-naive patients, driven by the calculation of SF, was determined to obtain 76% power at a one-sided 5% level of significance for showing superiority of granule formulation over DT formulation with respect to change from baseline to week 24 of treatment in SF. A sample size of 45 ICT-naive patients in each treatment arm would have 76% power to detect a difference in means of 450.0 ng/mL assuming that the common SD is 900.0 ng/mL using a two group t-test with a 0.050 one-sided significance level. For the co-primary endpoint, patient compliance to treatment, with 45 ICT-naive patients per treatment arm, the power to detect a difference of 10% or more in mean compliance was about 84%. Considering a potential of 5% dropout rate patients, the required sample size to achieve the primary objective was 48 ICT-naive patients for each treatment arm (96 patients in total).

The sample size for ICT pre-treated patients was based on the precision in the estimate of SF change after 48-weeks of treatment and on practical considerations. Considering that a direct comparison of granule and DT formulations in terms of efficacy was not foreseen in ICT pretreated patients, the required sample size was not based on power calculations. A maximum of 120 (60 patients in each treatment arms) ICT pre-treated patients were planned to be randomized. Sixty patients would provide an estimate of SF change with precision (half-width of 95% confidence interval) equal to 303.6.

Thus, the total required sample size for this clinical trial was up to 108 patients for each treatment arm (up to 216 patients in total), including 48 ICT-naive patients per group (96 ICT-naive patients in total).

Interim analysis

An interim analysis was performed with a data cut-off date (Nov 16, 2017), focusing on all randomized ICT-naive patients, who had completed a minimum of 12 weeks (≥84 days) of treatment exposure or discontinued from treatment core phase at the time of the cut-off date. Only descriptive analyses were performed; no modification of the design was triggered by the results of this interim analysis. No adjustment for multiplicity was considered.

Key changes in the conduct of the study

The first patient first visit occurred on October 21, 2015 and the key changes occurred after the commencement of the study are listed in the Table S2.

Results for ICT–pre-treated population

For the population of ICT–pre-treated patients, the mean compliance after 24 weeks in the deferasirox granules and deferasirox DT groups, respectively, was 86.4% and 84.8% (ANCOVA model). The difference between the treatment groups was 1.6% (95% CI, −3.3 to 6.6). The mean changes from baseline in SF after 24 weeks in the deferasirox granules and deferasirox DT groups, respectively, were 147.8 ng/mL and 188.1 ng/mL (ANCOVA model). The difference between the treatment groups was −40.3 ng/mL (95% CI, −377.5 to 296.9). The results of the compliance and SF changes from baseline analyses repeated in the ICT–pre-treated patients were similar to those of the ICT-naive and overall patient populations.

After 24 and 48 weeks, the mean compliance in the ICT–pre-treated patients was 91.2% and 90.4%, respectively, for deferasirox granules, and 88.5% and 87.1%, respectively, for deferasirox DT. After 24 and 48 weeks, mean changes from baseline in SF in the ICT–pre-treated patients were 150.3 ng/mL and 215.7 ng/mL, respectively, for deferasirox granules, and 59.0 ng/mL and 207.7 ng/mL, respectively, for deferasirox DT.

In ICT–pre-treated patients (N=115), the overall incidence of AE was similar with deferasirox granules and deferasirox DT (91.4% vs 94.7% respectively). The most commonly (≥20%) reported AE in the deferasirox granules and deferasirox DT groups, respectively, were pyrexia (24.1% and 26.3%), upper respiratory tract infection (24.1% and 33.3%), ALT increased (22.4% and 17.5%), and UPCR increased (27.6% and 43.9%). The profile was generally similar across the treatment groups, as no AE were noted with a difference of >10%, except for UPCR increased (27.6% and 43.9%), oropharyngeal pain (12.1% and 1.8%), vomiting (8.6% and 19.3%), and nausea (3.4% and 14.0%) in the deferasirox granules and DT groups, respectively.

In ICT–pre-treated patients, the incidence of AE leading to study drug discontinuation, regardless of study drug relationship, was low and similar in both treatment groups (5.2% vs 7.0%). The AE leading to study drug discontinuation were ALT increased, AST increased, headache, and drug reaction with eosinophilia and systemic symptoms in the deferasirox granules group and ALT increased, transaminases increased, Fanconi syndrome acquired, and rash in the deferasirox DT group.

Among ICT–pre-treated patients, 56.9% and 73.7% of patients in the deferasirox granules and DT groups, respectively, experienced an AE suspected to be study drug-related. In ICT–pre-treated patients, 60.3% and 71.9% patients in the deferasirox granules and DT groups, respectively, had an AE of special interest.

Tables and Figures

Table S1. Key changes in the conduct of the study

Date	Key changes
December 1, 2015	• Expansion of the study population by revising the inclusion criteria to allow for the enrollment of up to 120 patients who had prior history of ICT in addition to the 120 ICT-naive patients originally planned. This would allow the continuation of the study if the recruitment of ICT-naive patients became challenging to complete in a reasonable timeframe. • Addition of new objective to evaluate the change in SF in both populations (ICT-naive and ICT pre-treated patients).

August 24, 2016	• Addition of an optional extension phase to the existing study allowed the patients who participated and completed the 48-weeks core treatment phase as per protocol, and did not have access to the new formulation (granules or film coated tablets), the possibility to extend treatment with deferasirox granules for a maximum of 5 years after completing the core treatment phase or until there was local access to new formulation (granules or film coated tablets), whichever occurred first. Patients only who demonstrated benefit to granules or DT in the core phase, and/or expressed the wish to continue in the optional extension phase on granules were started in the optional extension phase.

December 6, 2017	• To modify the assessment time-point for the primary analysis (from change from baseline for SF and compliance after 48-weeks of treatment to after 24-weeks). A linear relationship between changes from baseline at 24 and 48-weeks of treatment was established based on a pool of representative randomized studies (CICL670A0105, CICL670A0107, CICL670A0109 and CICL670A2206) with SF available at 6 and 12-months for deferoxamine and deferasirox arms. This finding supported the use of the 6-month time-point as reliable surrogate for the 12-month time-point (Novartis data on file). Primary endpoints based on changes from baseline after 24-weeks of treatment allowed an earlier disclosure of primary analysis. The compliance (using drug count) was evaluated in pediatric patients over 6 months and 12 months for deferoxamine and deferasirox arms in the study ICL670A2206. The observed treatment effect over 6 months vs 12 months was similar. This suggested compliance over 6 months was accurate at predicting compliance over 12 months.

	• To reduce the sample size for the ICT-naive patients, following interactions with Health Authorities as the recruitment of ICT-naïve patients was much slower than anticipated due to the global availability of chelation therapies in these indications. It was discussed and agreed that the sample size for ICT naïve patients would be reduced to reflect the modification of primary endpoints. At least 96 ICT-naive patients were planned to be enrolled instead of 120 patients. This lower sample size would allow to obtain 76% power at a one-sided 5% level of significance for showing superiority of granule formulation over DT formulation with respect to change from baseline after 24-weeks of treatment in SF, assuming a dropout rate of 5%. This power was considered adequate to demonstrate targeted treatment effect, and would allow an earlier full recruitment of ICT-naïve patients in the study, and therefore an earlier disclosure of primary analysis. • The eligibility criteria for the extension phase were modified to allow patients who participated and completed 48-weeks of treatment in the core phase and for whom new formulation was not available to continue in the extension phase, if they derived clinical benefit from the study drug, as confirmed by investigator.

Table S2. List of Independent Ethics Committees (IEC) or Institutional Review Boards (IRB) by study center

Facility Name **Address** **Country**	**Ethics Committee or Institutional Review Board**
Chronic Care Center Hazmiyeh Beirut PO Box 213 Lebanon	Institutional Review Board of American University of Beirut
Siriraj Hospital Bangkok noi Bangkok 10700 Thailand	Human Research Protection Unit. Faculty of Medicine Siriraj Hospital, Mahidol University
Maharaj Nakhon Chiangmai Hospital Muang Chiangmai 50200 Thailand	Research Ethics Committee Faculty of Medicine, Chiang Mai University
Hospital Kuala Lumpur Kuala Lumpur 50586 Malaysia	Jawatankuasa Etika & Penyelidikan Perubatan (Medical Research & Ethics Committee)
Hospital Pulau Pinang Pulau Pinang 10990 Malaysia	Jawatankuasa Etika & Penyelidikan Perubatan (Medical Research & Ethics Committee)
Hospital Umum Sarawak Kuching Sarawak 93586 Malaysia	Jawatankuasa Etika & Penyelidikan Perubatan (Medical Research & Ethics Committee)
Hospital Raja Permaisuri Bainun Ipoh Perak Malaysia	Jawatankuasa Etika & Penyelidikan Perubatan (Medical Research & Ethics Committee)
St. Jude Children's Research Hospital Memphis Memphis TN 38105 United States	St. Jude Children's Research Hospital Institutional Review Board
Children's Hospital of Philadelphia Philadelphia PA 19104 United States	The Children's Hospital of Philadelphia IRB Office
Weill Cornell Medical College New York NY 10065 United States	Weill Cornell Medicine Institutional Review Board
Ann and Robert H. Lurie Children's Hospital of Chicago Chicago IL 60611 United States	Ann and Robert H. Lurie Children's Hospital of Chicago Institutional Review Board
UCSF Benioff Children's Hospital Oakland CA 94609 United States	UCSF Benioff Children's Hospital Oakland IRB
Children's Healthcare of Atlanta Atlanta GA 30342 United States	Emory University
Children's Hospital at Montefiore Bronx NY 10467	Biomedical Research Alliance of NY, LLC

United States	
Medical University of South Carolina Charleston SC 29425 United States	Medical University of South Carolina Institutional review Board for Human Research-IRB-III
Cliniques Universitaires Saint-Luc UCL Brussel 1200 Belgium	Comité d'Ethique
Universitair Ziekenhuis Antwerpen Edegem 2650 Belgium	Comité voor Medische Ethiek
UMHAT Tsaritsa Yoanna-ISUL EAD; Clinic of pediatric clinical hematology and oncology Sofia Bulgaria 1527 Bulgaria	ECMT (Ethic Committee for Multicenter Trials)
University Multifunctional Hospital for Active Treatment "Sveti Georgi" Plovdiv 4002 Bulgaria	ECMT (Ethic Committee for Multicenter Trials)
Multifunctional Hospital for Active Treatment "Sveta Marina" Varna 9010 Bulgaria	ECMT (Ethic Committee for Multicenter Trials)
E.O. Ospedali Galliera Genova GE 16128 Italy	Comitato Etico Regionale della Liguria
ARNAS Civico-Di Cristina-Benfratelli-P.O.Civic.e Benfratelli Palermo PA 90127 Italy	Comitato Etico Palermo 2
A.O. Ospedali Riuniti Villa Sofia-Cervello - P.O. Cervello Palermo PA 90146 Italy	Comitato Etico Palermo 2
Azienda Ospedaliera di Rilievo Nazionale A. Cardarelli Napoli 80131 Italy	Comitato Etico Cardarelli-Santobono
Debreceni Egyetem Klinikai Kozpont Debrecen 4032 Hungary	Egészségügyi Tudományos Tanács
Hôpital intercommunal de Créteil Créteil 94000 France	CPP « Ile de France III » - COCHIN
Hopital Necker Enfants Malades Paris Cedex 15 75743 France	CPP « Ile de France III » - COCHIN
Ege University Medical Faculty Izmir 35040 Turkey	Ege Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu

Cukurova University Medical Faculty Adana Turkey 01330 Turkey	Ege Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu
Hacettepe University Medical Faculty Ankara 06100 Turkey	Ege Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu
Philippine Children's Medical Center Quezon City Philippines 1100 Philippines	Philippine Children's Medical Center, Institutional Review Board-Ethics Committee (IRBEC)
Sultan Qaboos University Muscat 123 Oman	SQUH Medical Research Center
Hospital de Especialidades Pediátricas, Caja Seguro Social Panama City Republica de Panama Panama	Comité Institucional de Ética de la Investigación de la Caja del Seguro Social
Center of Children's Hematology n.a. D. Rogachev Moskow 117198 Russia	Independent Ethics Committee of FGBU «FNKC DGOI n.a. D. Rogachev»
Clinical Research Center, Faculty of Medicine, Alexandria University. Alexandria Alexandria 21563 Egypt	Clinical Research Center, Faculty of Medicine, Alexandria University.
Pediatric Heomatology department Centre De Greffe De Moelle Osseuse Tunis Rue jebel lakhdhar Tunis 1006 Tunisia	Le Commite d'Ethique local l'Hopital Charles Nicolle
Institute of Child Health Kolkata 700017 India	Institutional Ethics Committee

Table S3. mSICT questionnaire domain scores for both ObsRO and PRO for the overall population

	All patients, mean (SD)			
	Deferasirox granules (N=112)		Deferasirox DT (N=112)	
	Week 25	EOT-core	Week 25	EOT-core
ObsRO questionnaire mean score (SD)*: caregiver's perspective				
Adherence (low score=better)	6.5 (1.7)	6.8 (2.6)	7.1 (2.4)	7.5 (2.5)
Concerns (high score=fewer concerns)	4.5 (0.9)	4.6 (0.8)	4.3 (1.0)	4.0 (1.2)
ObsRO questionnaire mean score (SD)*: child perspective	9.1 (2.6)	9.1 (3.0)	11.1 (3.8)	11.3 (4.0)
Adherence (low score=better)	8.7 (1.9)	9.0 (1.8)	8.6 (1.9)	8.8 (1.8)
Concerns (high score=fewer concerns)				
PRO questionnaire mean score (SD)†				
Adherence (low score=better)	9.2 (3.3)	8.4 (2.3)	11.9 (3.9)	12.9 (4.2)
Satisfaction/preference (low score=better)	3.0 (1.1)	3.1 (0.9)	5.5 (2.4)	4.8 (2.2)
Concerns (high score=fewer concerns)	14.5 (1.2)	13.5 (2.8)	11.5 (3.1)	12.8 (2.2)

*For deferasirox granules and DT, respectively, n=53 and n=61 at week 25, and n=54 and n=60 at EOT-core.

†For deferasirox granules and DT, respectively, n=11 and n=13 at week 25, and n=15 and n=13 at EOT-core.

The number of patients with available data was very small; therefore, results should be interpreted with caution.

DT, dispersible tablet; EOT, end of treatment; mSICT, modified Satisfaction with Iron Chelation Therapy; ObsRO, observer-reported outcome; PRO, patient-reported outcome; SD, standard deviation.

Table S4. Palatability ObsRO/PRO: summary of palatability summary score by visit and treatment

		PRO questionnaire		ObsRO questionnaire	
Visit	**Statistics**	**Deferasirox granules N=112**	**Deferasirox DT N=112**	**Deferasirox granules N=112**	**Deferasirox DT N=112**
Week 2	**n**	**15**	**13**	**62**	**68**
	Mean	10.3 (1.9)	8.8 (3.3)	10.9 (0.9)	8.9 (3.1)
Week 3	**n**	**17**	**16**	**72**	**72**
	Mean	10.9 (0.2)	9.6 (2.8)	10.8 (0.8)	9.4 (2.9)
Week 25	**n**	**11**	**13**	**52**	**61**
	Mean (SD)	10.4 (1.8)	9.2 (2.7)	10.6 (1.7)	9.3 (2.8)
Change from week 2 to week 25	**n**	**10**	**9**	**39**	**51**
	Mean (95% CI)	−0.4 (−1.9 to 1.1)	1.3 (−1.2 to 3.9)	−0.0 (−0.6 to 0.5)	0.7 (−0.2 to 1.6)
	SD	2.1	3.3	1.7	3.2
EOT-core	**n**	**14**	**13**	**53**	**60**
	Mean (SD)	11.0 (0.0)	9.4 (3.1)	10.9 (1.0)	9.0 (3.1)
Change from week 2 to EOT-core	**n**	**11**	**9**	**42**	**48**
	Mean	0.7 (−0.7 to	0.9 (−2.3 to	0.2 (−0.1 to 0.5)	0.4 (−0.8
	SD	2.1	4.2	1.1	3.9

CI, confidence interval; DT, dispersible tablet; EOT, end of treatment; ObsRO, observer-reported outcome; PRO, patient-reported outcome; SD, standard deviation.

Safety

The most commonly noted AESI groups in the core phase were: liver disorders (32.7% vs. 35.1%) and renal disorders (30.9 vs. 40.5%, Online Supplementary Table S5).

In the overall patient population, the number of patients who experienced AE suspected to be related to the study drug was similar between both the treatment groups (deferasirox granules, 52.7%; deferasirox DT, 57.7%). Apart from UPCR increases (deferasirox granules, 20.0%; deferasirox DT, 27.9%) and alanine aminotransferase increases (deferasirox granules, 10.9%; deferasirox DT, 7.2%), all other AE suspected to be study drug-related were reported in <10% of patients (in either of the treatment groups) (Online Supplementary Table S6). Among ICT-naive patients, 48.1% and 40.7% of patients in the deferasirox granules and DT groups experienced an AE suspected to be study drug-related.

The overall incidence of serious AE was similar in both the treatment groups (deferasirox granules, 24.5%; deferasirox DT, 20.7%) (Online Supplementary Table S7). Apart from pyrexia (3.6% in each treatment group), sickle cell anemia with crisis (2.7% and 4.5%), pneumonia (0.9% and 2.7%), and bronchitis (0 and 2.7%), all the serious AE were reported in either one or two patients in the deferasirox granules and deferasirox DT groups, respectively. No deaths were observed in this study.

In the overall and ICT-naive populations, respectively, 48.2% and 46.2% of patients in the deferasirox granules group and 62.2% and 59.3% patients in the DT group had an AE that required dose adjustment/interruption (Online Supplementary Table S8).

A similar proportion of patients in the deferasirox granules and deferasirox DT groups in the overall patient population reported adverse events of special interest (AESI; 59.1% and 61.3%, respectively) (Online Supplementary Table S9). The incidence of AESI of renal disorders in the deferasirox granules and deferasirox DT groups was 31.8% and 42.3%, respectively, and in the majority of patients (28.2% and 35.1%) these AESI were suspected to be study drug-related by the study investigator. The incidence of AESI in the deferasirox granules and DT groups in ICT-naive patients was 57.7% and 50.0%, respectively. None of the AESI groups were noted with a difference of >5% between the treatment groups.

In the overall patient population, two patients (1.8%) in the deferasirox DT group had a serum creatinine post-baseline shift within the notable range (two consecutive values >upper limit of normal and >33% increase from baseline), whereas none of the patients in the deferasirox granules group had a post-baseline shift to the notable range. One patient from the deferasirox DT group had UPCR within the notable range post-baseline (two consecutive values >1.0 mg/mg), while three patients from the deferasirox granules group had UPCR within the notable range. Among patients from the deferasirox DT group, eight (7.2%) and two (1.8%) patients had alanine aminotransferase and aspartate aminotransferase increases, respectively, within the notable range (>5 x upper limit of normal and 2 x baseline value), whereas 11 (10.0%) and three (2.7%) patients from the deferasirox granules group had alanine aminotransferase and aspartate aminotransferase increases, respectively, within the notable range.

Vital signs, ocular examinations, growth velocity, and pubertal stage analysis did not reveal any clinical relevance in either of the treatment groups. In the overall patient population, post-baseline two patients had mild left ventricular dilation (neither suspected to be study drug related; one resolved after 38 days). In the overall patient population, one patient from each of the granules and DT groups was observed to have post-baseline, clinically significant abnormalities in audiometric examinations (both suspected to be study drug related; one resolved after 44 days).

Table S5. Adverse events leading to study drug discontinuation (overall and severe AE), regardless of study drug relationship, by preferred term and treatment during the core phase

	Deferasirox granules N=110		Deferasirox DT N=111	
Preferred term	**All AE n (%)**	**Severe AE n (%)**	**All AE n (%)**	**Severe AE n (%)**
Any preferred term - Total	**5 (4.5)**	**3 (2.7)**	**8 (7.2)**	**5 (4.5)**
Transaminases increased	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)
Increased ALT	1 (0.9)	0	1 (0.9)	1 (0.9)
Drug reaction with eosinophilia and systemic symptoms	1 (0.9)	1 (0.9)	0	0
Upper gastrointestinal hemorrhage	1 (0.9)	1 (0.9)	0	0
Blood creatinine increased	0	0	1 (0.9)	1 (0.9)
Fanconi syndrome acquired	0	0	1 (0.9)	1 (0.9)
Rash	0	0	1 (0.9)	1 (0.9)
Increased AST	1 (0.9)	0	0	0
Headache	1 (0.9)	0	0	0
Bilirubin conjugated increased	0	0	1 (0.9)	0
Proteinuria	0	0	1 (0.9)	0
Vomiting	0	0	1 (0.9)	0

AE, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DT, dispersible tablet.

Table S6. Adverse events ([≥5%], overall and severe AE) suspected to be study drug-related by preferred term and treatment during the core phase

	Deferasirox granules N=110		Deferasirox DT N=111	
Preferred term	**All AE n (%)**	**Severe AE n (%)**	**All AE n (%)**	**Severe AE n (%)**
Any preferred term - Total	**58 (52.7)**	**15 (13.6)**	**64 (57.7)**	**14 (12.6)**
UPCR increased	22 (20.0)	2 (1.8)	31 (27.9)	4 (3.6)
ALT increased	12 (10.9)	5 (4.5)	8 (7.2)	5 (4.5)
Bilirubin conjugated increased	5 (4.5)	0	10 (9.0)	0
Proteinuria	9 (8.2)	1 (0.9)	6 (5.4)	1 (0.9)
Transaminases increased	8 (7.3)	5 (4.5)	6 (5.4)	3 (2.7)
AST increased	7 (6.4)	3 (2.7)	6 (5.4)	1 (0.9)

AE, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DT, dispersible tablet; UPCR, urinary protein/creatinine ratio.

Table S7. SAE (overall and severe AE), regardless of study drug relationship by preferred term and treatment during the core phase (two or more patients in any treatment)

	Deferasirox granules N=110		Deferasirox DT N=111	
Preferred term	**All AE n (%)**	**Severe AE n (%)**	**All AE n (%)**	**Severe AE n (%)**
Any preferred term - Total	**27 (24.5)**	**16 (14.5)**	**23 (20.7)**	**18 (16.2)**
Sickle cell anemia with crisis	3 (2.7)	3 (2.7)	5 (4.5)	5 (4.5)
Pyrexia	4 (3.6)	3 (2.7)	4 (3.6)	2 (1.8)
Pneumonia	1 (0.9)	0	3 (2.7)	3 (2.7)
Bronchitis	0	0	3 (2.7)	3 (2.7)
Bronchiolitis	2 (1.8)	1 (0.9)	0	0
Dengue fever	2 (1.8)	1 (0.9)	1 (0.9)	1 (0.9)
Gastroenteritis	2 (1.8)	1 (0.9)	0	0
Upper gastrointestinal hemorrhage	2 (1.8)	2 (1.8)	0	0
Anemia	1 (0.9)	1 (0.9)	2 (1.8)	2 (1.8)
Influenza	0	0	2 (1.8)	2 (1.8)
Tonsillitis	0	0	2 (1.8)	2 (1.8)
Viral infection	0	0	2 (1.8)	0

AE, adverse events; DT, dispersible tablet; SAE, serious adverse events.

Table S8. Adverse events requiring dose adjustment or study drug interruption (overall and severe AE), regardless of study drug relationship, by preferred term and treatment during the core phase (≥2 patients in either of the treatment groups)

	Deferasirox granules N=110		**Deferasirox DT N=111**	
	All AE n (%)	**Severe AE n (%)**	**All AE n (%)**	**Severe AE n (%)**
Any preferred term -Total	**53 (48.2)**	**15 (13.6)**	**69 (62.2)**	**23 (20.7)**
UPCR increased	12 (10.9)	4 (3.6)	20 (18.0)	3 (2.7)
Bilirubin conjugated increased	10 (9.1)	0	16 (14.4)	0
Pyrexia	8 (7.3)	0	11 (9.9)	2 (1.8)
Increased ALT	10 (9.1)	6 (5.5)	9 (8.1)	7 (6.3)
Increased AST	7 (6.4)	3 (2.7)	4 (3.6)	1 (0.9)
Proteinuria	7 (6.4)	1 (0.9)	5 (4.5)	1 (0.9)
Transaminases increased	4 (3.6)	4 (3.6)	6 (5.4)	4 (3.6)
Diarrhea	4 (3.6)	0	1 (0.9)	0
Rash	1 (0.9)	0	4 (3.6)	1 (0.9)
Upper respiratory tract infection	2 (1.8)	0	4 (3.6)	0
Pneumonia	1 (0.9)	0	3 (2.7)	3 (2.7)
Viral infection	2 (1.8)	0	3 (2.7)	0
Blood bilirubin increased	2 (1.8)	0	3 (2.7)	0
Tonsillitis	3 (2.7)	0	1 (0.9)	0
Abdominal pain	3 (2.7)	0	0	0
Gastroenteritis	1 (0.9)	0	2 (1.8)	0
Vomiting	0	0	2 (1.8)	0
Pharyngitis	2 (1.8)	0	0	0
Oropharyngeal pain	2 (1.8)	0	0	0

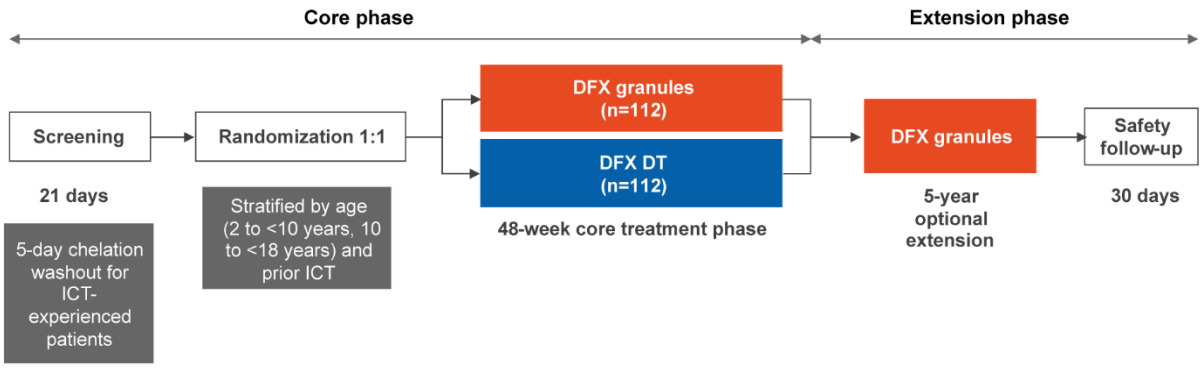
AE, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DT, dispersible tablet; UPCR, urinary protein/creatinine ratio.

Table S9. Adverse events of special interest, regardless of study drug relationship, by grouping, preferred term, and treatment during the core phase with a ≥5% in either of the treatment groups

Group term (Risk name) Preferred term	Deferasirox granules N=110 n (%)	Deferasirox DT N=111 n (%)
Any adverse event of special interest - Total	**65 (59.1)**	**68 (61.3)**
Increased liver transaminases	**36 (32.7)**	**39 (35.1)**
ALT increased	20 (18.2)	15 (13.5)
Bilirubin conjugated increased	12 (10.9)	16 (14.4)
AST increased	12 (10.9)	11 (9.9)
Transaminases increased	9 (8.2)	8 (7.2)
Peripheral blood cytopenias	**5 (4.5)**	**7 (6.3)**
Renal disorders - Proteinuria	34 (30.9)	45 (40.5)
UPCR increased	27 (24.5)	38 (34.2)
Proteinuria	9 (8.2)	8 (7.2)

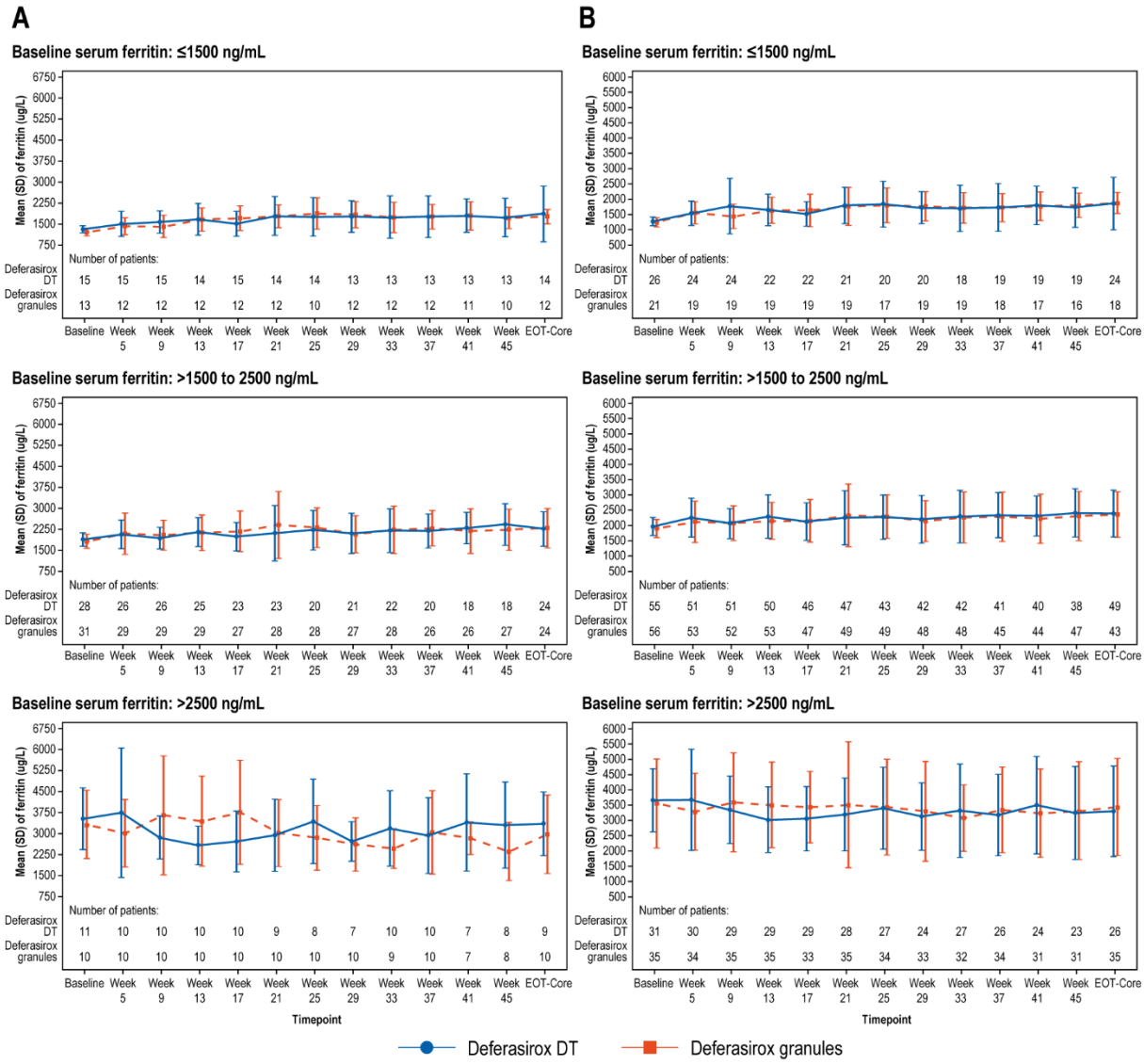
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DT, dispersible tablet; UPCR, urinary protein/creatinine ratio.

Figure S1. CALYPSO Study design



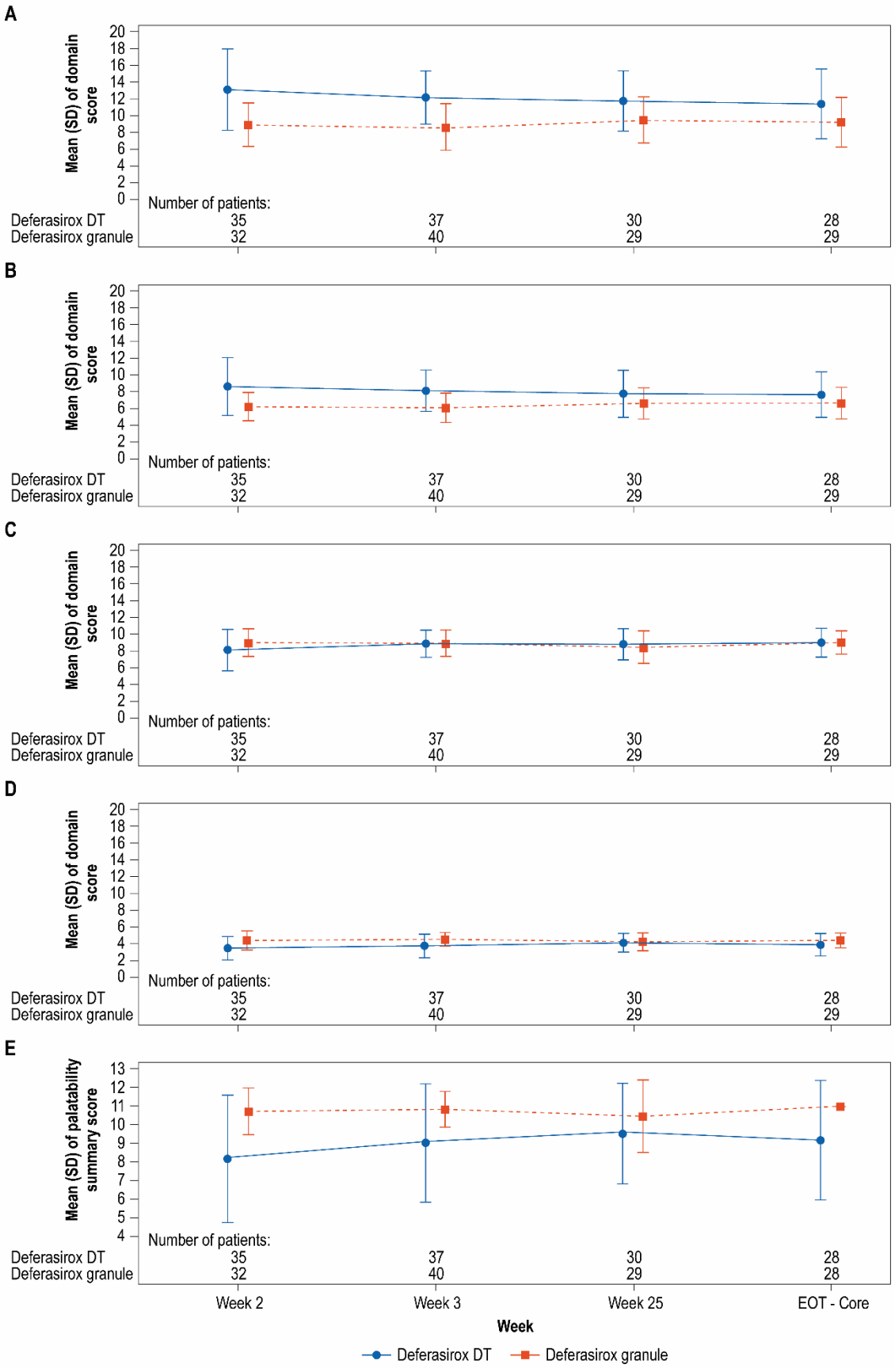
DFX, deferasirox; DT, dispersible tablet; ICT, iron chelation therapy

Figure S2. Serum ferritin (ng/mL) mean (SD) by time point and treatment during the core phase - subgroup defined by baseline serum ferritin levels. (A) ICT-naive. (B) Overall patient population



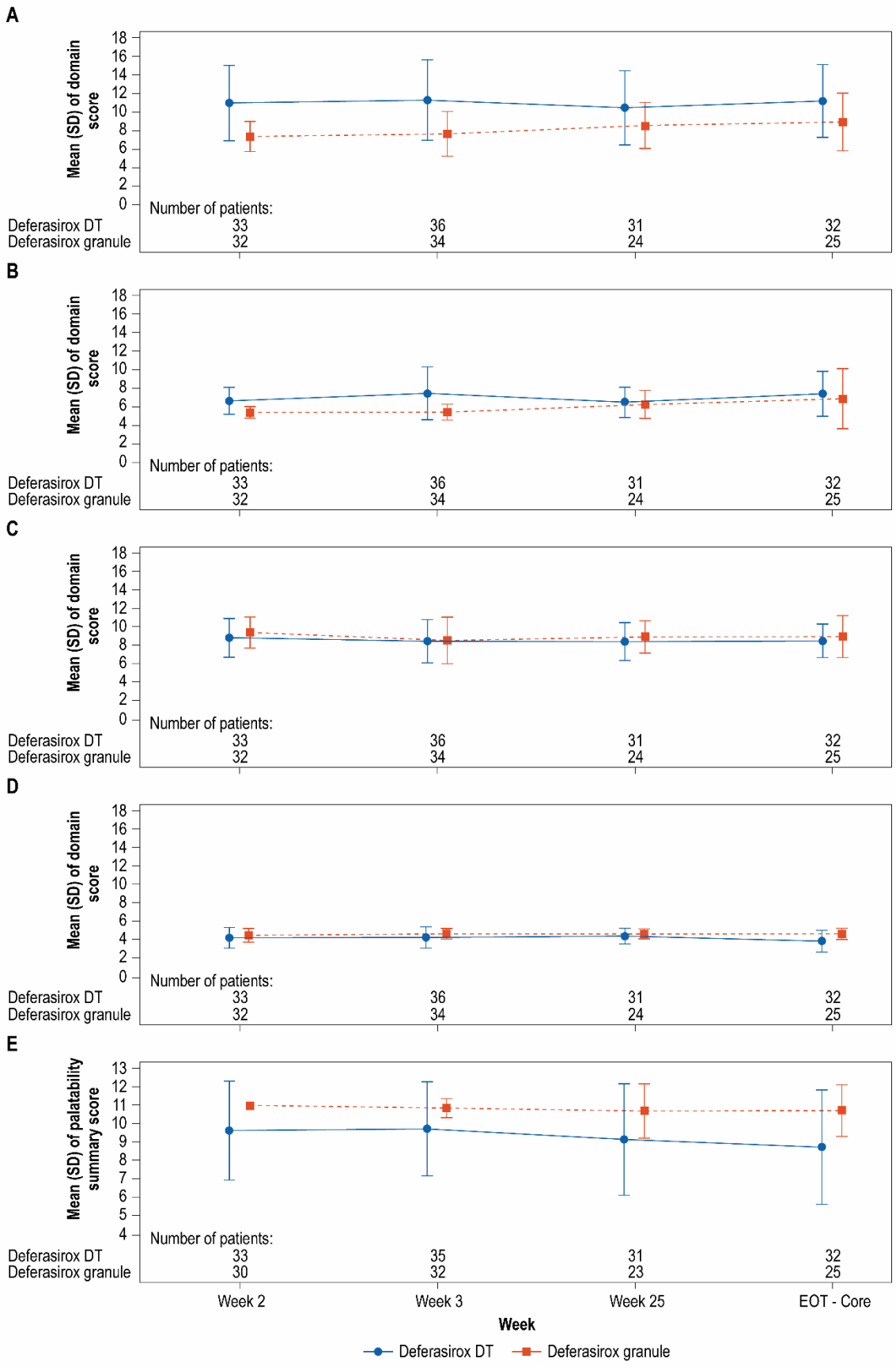
DT, dispersible tablet; ICT, iron chelation therapy; SD, standard deviation

Figure S3. PRO/ObsRO questionnaires (ICT-naive 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


A
B
C
D
E
Mean (SD) of domain score
Mean (SD) of palatability summary score
Number of patients:
Deferasirox DT 35 37 30 28
Deferasirox granule 32 40 29 29
Deferasirox DT 35 37 30 28
Deferasirox granule 32 40 29 28
Week 2
Week 3
Week 25
EOT - Core
Week
Deferasirox DT
Deferasirox granule

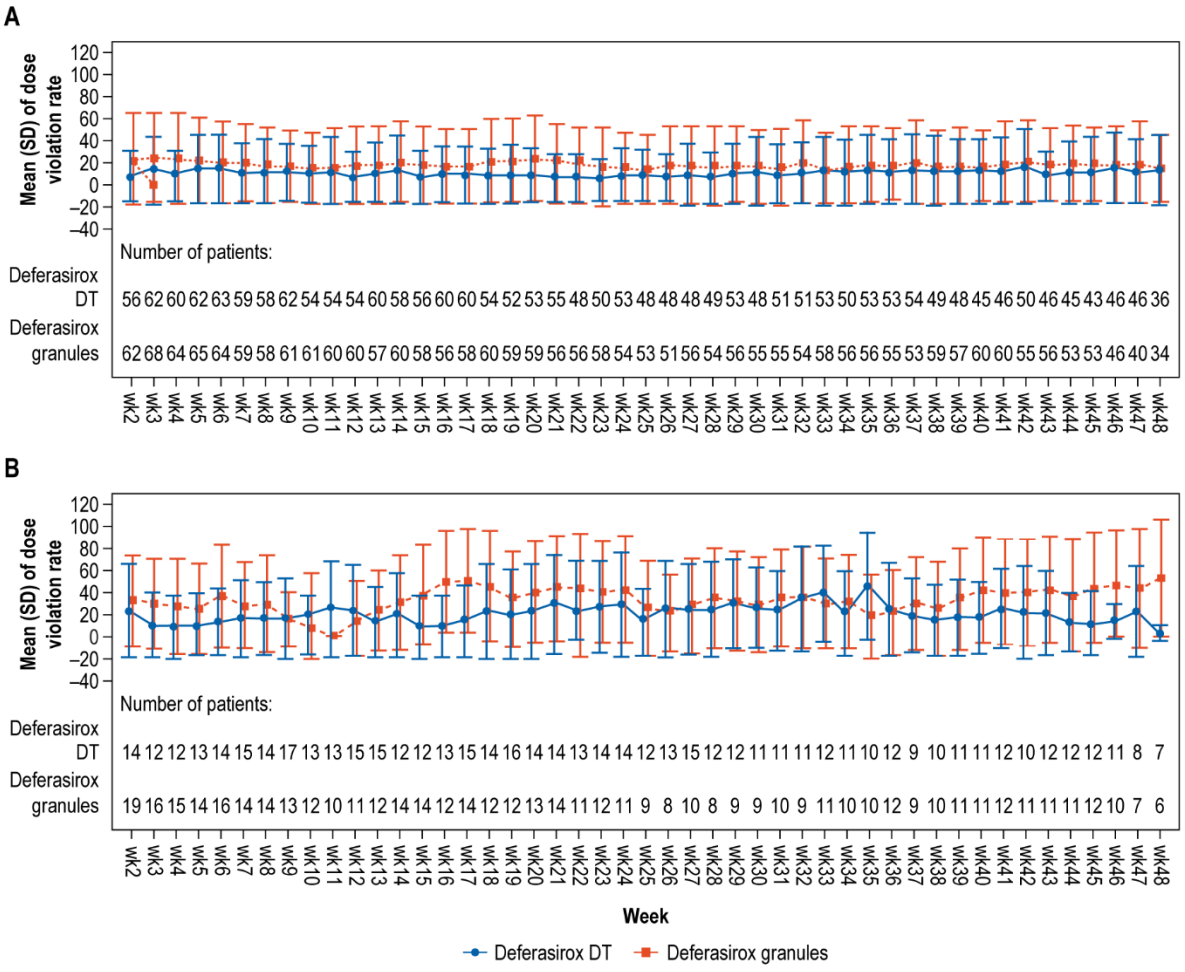
DT, dispersible tablet; EOT, end of treatment; Modified SICT, modified satisfaction with iron chelation therapy; ObsRO, observer-reported outcome; PRO, patient reported outcome; SD, standard deviation.

Figure S4. PRO/ObsRO questionnaires (ICT-pretreated 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


A
Mean (SD) of domain score
18
16
14
12
10
8
6
4
2
0
Number of patients:
Deferasirox DT 33 36 31 32
Deferasirox granule 32 34 24 25
B
Mean (SD) of domain score
Number of patients:
Deferasirox DT 33 36 31 32
Deferasirox granule 32 34 24 25
C
Mean (SD) of domain score
Number of patients:
Deferasirox DT 33 36 31 32
Deferasirox granule 32 34 24 25
D
Mean (SD) of domain score
Number of patients:
Deferasirox DT 33 36 31 32
Deferasirox granule 32 34 24 25
E
Mean (SD) of palatability summary score
13
12
11
10
9
8
7
6
5
4
Number of patients:
Deferasirox DT 33 35 31 32
Deferasirox granule 30 32 23 25
Week 2
Week 3
Week 25
EOT - Core
Week
Deferasirox DT
Deferasirox granule

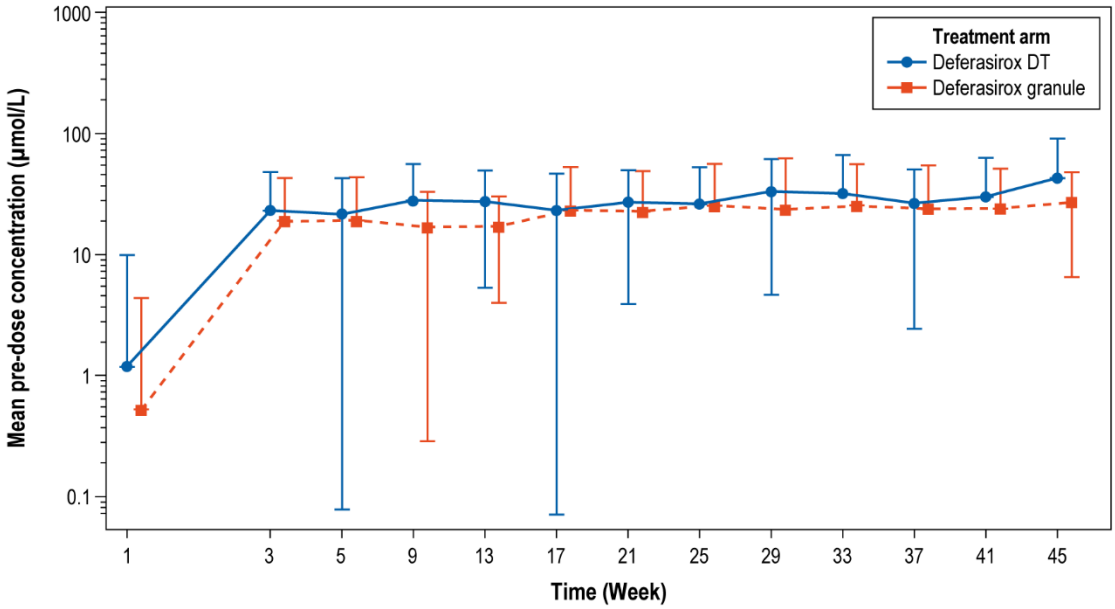
DT, dispersible tablet; EOT, end of treatment; Modified SICT, modified satisfaction with iron chelation therapy; ObsRO, observer-reported outcome; PRO, patient reported outcome; SD, standard deviation.

Figure S5. Compliance diary: weekly dose violation rate mean (SD) over time by treatment. (A) ObsRO questionnaire. (B) PRO questionnaire



DT, dispersible tablet; ObsRO, observer-reported outcome; PRO, patient/observer-reported outcome; SD, standard deviation

Figure S6. Arithmetic mean (SD) dose-adjusted pre-dose concentration overtime by treatment (PAS-1)



Number of patients:													
Deferasirox DT	95	55	65	65	59	56	57	51	53	56	51	54	52
Deferasirox granules	92	71	69	67	61	52	60	55	53	55	57	55	55

	Deferasirox granules	Deferasirox DT
Number of samples	802	743
Variance between predicated and observed steady-state pre-dose concentrations	700.6	1370.9

DT, dispersible tablet; SD, standard deviation