DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF HEMATOLOGY PRODUCTS

MEDICAL OFFICER'S REVIEW

NDAs:	21882 Supplement 028, 206910 Supplement 009, 207968 Supplement 004
Sponsor:	Novartis One Health Plaza East Hanover, NJ 07936
Drug name:	Exjade® (Deferasirox)
Indication:	Iron Overload
Route of Administration:	Oral (PO)
Submission:	NDA 21882 Supporting Document 1134, NDA 206910 Supporting Document 440, NDA 207968 Supporting Document 112 (Submission of Pediatric Study Reports- Pediatric Exclusivity Determination Requested)
Date submitted:	June 15, 2018
Review completed:	November 29, 2018
Reviewer:	Andrew Dmytrijuk M.D.

I. Background

In NDA 21882 supporting document 1134 letter date letter date June 15, 2018 (received June 15, 2018) the sponsor submitted a report for study CICL670F2202 (F2202), titled "A Randomized, Open-Label, Multicenter, Two Arm, Phase 2 Study to Evaluate Treatment Compliance, Efficacy And Safety Of An Improved Deferasirox Formulation (Granules) In Pediatric Patients With Iron Overload", and requests pediatric exclusivity determination for deferasirox. The sponsor states, and I agree, that the information from study F2202 and the request for pediatric exclusivity determination for deferasirox extends to all the approved formulations of deferasirox, i.e., Exjade® tablets for Oral suspension (accelerated approval for marketing granted under NDA 21882), Jadenu® Tablets, for oral use (accelerated approval granted under NDA 206910) and Jadenu® Sprinkle granules for oral use (accelerated approval for marketing granted under NDA 207968). The sponsor's request for determination of pediatric exclusivity for deferasirox (under NDAs 21882, 206910 and NDA 207968) was discussed with the Pediatric Exclusivity Board on October 24, 2018.

Deferasirox (Exjade®, dispersible tablets) is an orally administered iron chelator that was granted accelerated approval for the treatment of iron overload due to chronic transfusion in patients with anemia ages 2 years and older on November 2, 2005 under NDA 21882. Exjade was also granted accelerated approval for the treatment of chronic iron overload in patients 10 years of age and older with non-transfusion dependent thalassemia (NTDT) syndromes and with a liver iron (Fe) concentration (LIC) of at least 5 mg Fe per gram of dry weight and a serum ferritin greater than 300 mcg/L on January 23, 2013 under NDA 21882. Deferasirox (Jadenu®, film coated tablets) were granted accelerated approval for marketing on March 30, 2015 under NDA 206910. Deferasirox (Jadenu Sprinkle®, granules) were granted accelerated approval for marketing on May 18, 2017 under NDA 207968. All three formulations of deferasirox, i.e., Exjade, Jadenu and Jadenu Sprinkle, have the same indications. On February 18, 2014 as part of a Proposed Pediatric Study Request (PPSR) submission the sponsor submitted protocol CICL670F2202 (F2202) titled, "A Randomized, Open-Label, Multicenter, Two Arm, Phase 2 Study to Evaluate Treatment Compliance, Efficacy and Safety of an Improved Deferasirox Formulation (Granules) in Pediatric Patients with Iron Overload." The submission was reviewed by Dr. George Shashaty (final signature date May 19, 2014). Following internal discussions including discussions with the Pediatric Research Committee (PeRC) a Pediatric Written Request (WR) was issued December 17, 2014. The WR acknowledges compliance as a significant issue for patients taking iron chelators and stated, "An increase in compliance due to a more palatable iron chelator formulation may improve the reduction in body iron burden during therapy, as demonstrated by a decrease in serum ferritin over time, for this patient group..." The WR outlined a single clinical study based on the F2202 protocol and stated under the section titled, "Clinical Studies" that patients must be chelation naïve.

Clinical review of the original study protocol F2202 was completed by Dr. George Shashaty in the Division of Hematology Products (DHP) final signature date May 19, 2014. The sponsor submitted an amended study F2202 (version 00 dated February 6, 2015) under IND 58554 letter date February 10, 2015 (received February 10, 2015). Clinical review of the amended protocol F2202 (version 00 dated February 6, 2015) was completed by Dr. Andrew Dmytrijuk in DHP final signature date September 9, 2015.

A Type C Meeting was held with the sponsor on July 14, 2017 to discuss the updates taken to accelerate enrollment of chelation naïve patients in Study F2202 and the path forward to fulfilling the Pediatric WR. The sponsor subsequently submitted a series of requests to modify the WR. The list of proposed WR amendments and the sponsor's rationale supporting the WR amendments are summarized in Appendix 2 in this review.

The most recent version of the F2202 protocol was submitted under IND 58554 supporting document 869 letter date January 5, 2018 (received January 5, 2018). The amended study F2202 (version 05 dated December 6, 2017) is summarized below in the Summary of Amended study F2202 (version 05 dated December 6, 2017) in this review. A synopsis of the amended study F2202 (version 05 dated December 6, 2017) is in Appendix 1 of this review for reference. Efficacy and safety results submitted under NDA 21882 supporting document 1134 letter date June 15, 2018 (received June 15, 2018) from study F2202 are reviewed in the section Efficacy and Safety Results from Study F2202 in this review. The sponsor's proposed wording changes to the deferasirox (Exjade, Jadenu and Jadenu Sprinkle) products Labels are discussed in the section Sponsor Proposed Exjade, Jadenu and Jadenu Sprinkle Labeling Changes.

Key Regulatory Milestones for Deferasirox Pediatric Submissions

The following list summarizes the key regulatory milestones for the sponsor's request for Pediatric Exclusivity for deferasirox.

- February 18, 2014 - Proposed Pediatric Study Request (PPSR) submitted for study F2202.
- June 9, 2014 - Inadequate Study Request issued – and stated if compliance is improved with the granule formulation compared to the dispersible tablet that the information from the study would result in a change in the available formulation but would not result in any clinically meaningful revisions to the pediatric information in the label and the study data would not improve the efficacy and safety of the use of deferasirox in the pediatric population. Revise the concomitant medication sections to be consistent with the approved labeling for Exjade and enhance PK sampling.
- December 17, 2014 – the original WR issued stated that not only the sponsor should complete F2202 but also address PMR750-1 (which was

the deferasirox 5 year registry study A2411 (which was in part the subject of recent labeling changes that were incorporated as part of a Tracked Safety Issue (TSI) regarding renal and hepatic toxicity (supplement-25)). The WR highlighted that patients must be chelation therapy naïve and that a sufficient number of patients must be enrolled to ensure that the study is adequately powered to detect a statistically significant and clinically relevant improvement in compliance and difference in change in serum ferritin from baseline to 48 weeks.

- July 14, 2017 – meeting was held with the sponsor to modify the WR to possibly increase enrollment but the sponsor primarily wanted to include more patients who were previously treated with iron chelation therapy.
- January 5, 2018 – the sponsor submitted the final version of study F2202 and interim results were submitted June 15, 2018 which focuses on the results from 71 chelation therapy naïve pediatric patients enrolled in F2202 and is the basis of this review.

Summary of Amended Study F2202 (version 05 dated December 6, 2017)

Briefly, the objective of study F2202 is to evaluate patient compliance (using stick pack or tablet counts) and change in serum ferritin over time for two formulations of deferasirox, i.e., the new granule formulation (claimed to have a better taste) and the approved dispersible tablet (DT) formulation. Study F2202 is a randomized (1:1), open-label, multicenter, two arm, phase II study to evaluate treatment compliance and change in serum ferritin of a new deferasirox granule formulation and the approved deferasirox DT formulation in children and adolescents aged ≥ 2 and < 18 years at enrollment with any transfusion-dependent anemia requiring chelation therapy due to iron overload, to demonstrate the effect of improved compliance on iron burden. At least 216 (96 treatment naive and 120 pretreated patients per treatment arm) male and female children and adolescent patients would be enrolled. The key inclusion criteria are as follows.

- Iron chelation therapy (ICT)-naïve and previously treated male and female children and adolescents ages ≥ 2 and < 18 years.
- Any transfusion-dependent anemia associated with iron overload requiring iron chelation therapy and with a history of transfusion of at least 20 packed red blood cell (PRBC) units, and a treatment goal of reduction, not maintenance of iron burden as measured by serum ferritin.
- Serum ferritin > 1000 ng/mL, measured at screening Visit 1 and screening Visit 2 (the mean value will be used for eligibility criteria).
- The study treatment duration will be 48 weeks.

Study drug dosing would be according to the approved product label. The co-primary efficacy endpoints are as follows. Descriptive statistics will be used to analyze efficacy and safety endpoints.

- Compliance measured by stick pack/tablet count pediatric ICT naïve patients with iron overload after 24 weeks of treatment. Compliance will be measured by stick pack/tablet count: it will be performed by study personnel every 4 weeks (week 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45 and end of treatment) based on the amount of medication dispensed, returned and reported as lost/wasted by the patient / caregiver
- Change from baseline in serum ferritin at 24 weeks of treatment. Serum ferritin testing will be performed at Screening Visits 1 and 2 and every 4 weeks from week 5 till end of treatment visit. Compliance will be measured by stick pack/tablet count every 4 weeks. The change in serum ferritin will be assessed at weeks 24 and 48 weeks.

Key changes made to the protocol in the amended study F2202 (version 05 dated December 6, 2017) submitted under IND 58554 supporting document 869 letter date January 5, 2018 compared to the protocol reviewed by Dr. Dmytrijuk final signature date September 9, 2015 are summarized below:

- Number of patients: Previously the sponsor proposed to enroll 80 patients (40 patients per treatment arm). Currently the sponsor proposes to enroll 216 patients (96 iron chelation therapy naïve patients and 120 patients previously treated with iron chelation therapy).
- Treatment duration: Previously the sponsor proposed a 24-week treatment duration for primary efficacy analysis. Currently the sponsor proposes a 48-week treatment duration.
- Primary efficacy endpoint: Previously the primary efficacy endpoint was the relative consumed stick pack /tablet count defined as the ratio of total count consumed to total count prescribed. Currently the sponsor proposes co-primary efficacy endpoints based on compliance measured by stick pack/tablet count and change from baseline in serum ferritin at 24 weeks of treatment. Secondary endpoints include compliance measured by stick pack/tablet count and change from baseline in serum ferritin at 48 weeks of treatment.
- Pharmacokinetic sampling: The sponsor previously proposed Optimal Sparse pharmacokinetic (PK) sampling. The sponsor currently proposes a Revised Sparse PK sampling method. The sponsor's revised sparse PK sampling is described below.

Reviewer comment: Study F2202 is reasonably well designed to evaluate patient compliance (using stick pack or tablet counts) and change in serum ferritin over time (48 weeks of deferasirox therapy and primary endpoint efficacy analysis at 24 weeks) for the two formulations of deferasirox, i.e., the new granule formulation (claimed to have a better taste) and the approved dispersible tablet (DT) formulation provided that sufficient ICT-naïve patients are enrolled to show a clinically meaningful change in serum ferritin. Key changes between versions for Study F2202 are summarized in Appendix 2 of this review.

II. Study F2202 Results

The clinical study report was submitted under NDA 21882 supporting document 1123 (letter date March 30, 2018 and received March 30, 2018). As of the data cut-off (November 16, 2017), 206/216 subjects were enrolled which included includes 90/96 ICT naive subjects and 116/120 ICT pre-treated subjects. Although the trial enrolled iron chelation therapy (ICT) pre-treated subjects and ICT naive subjects, the data submitted in the study report for study F2202 focuses on all randomized ICT naive subjects, who have completed a minimum of 12 weeks (≥ 84 days) of treatment exposure or discontinued from treatment prior to week 48 of deferasirox therapy at the time of the cut-off date.

Disposition

The efficacy analysis set includes 71/96 patients and the safety set includes 70/96 ICT-naïve patients. One patient, randomized to receive granules, was excluded from the iron chelation therapy treatment naïve safety set because they were not treated with study drug. There were 28 patients who completed the core phase of the study. There were 3 patients who were discontinued from the study due to adverse events (AEs), i.e., two due to vomiting/proteinuria and one due to upper gastrointestinal bleeding. There were 5 patients who were discontinued from the study due to protocol deviation, lack of efficacy, physician decision or parent/patient decision. Protocol deviations were reported in 57/71 (80%) patients. The most commonly cited reason for protocol deviation in ≥ 20% of patients was ocular exam not performed (44/71, 62%), echocardiogram not performed (16/71, 23%) and patient reported outcome/observer reported outcome not performed (16/71, 23%). The reviewer's table below summarizes the patient disposition for 71 ICT-naïve patients included in the study F2202 report.

Table 1. Study F2202 Disposition

Disposition	N=71 (n,%)
Randomized and not treated	1 (1%)
Completed Core (48 weeks+ 30 day F/U)	28 (39%)
Discontinued Treatment	
AE	3 (4%)
Protocol dev, Recovery, Lack of Efficacy, Physician decision, Parent/Patient decision (n=1 each)	5 (7%)
Treatment Ongoing	34 (48%)

Reviewer's table derived from F2202 study report (NDA 21882 supporting document 1134 letter date June 15, 2018 (received June 15, 2018))

Demographics

The demographics of the 71 patients enrolled in study F2202 as of the data cut-off date (November 16, 2017) are shown in the reviewer's table below. There were 36 patients enrolled in the dispersible tablet treatment group and 35 patients enrolled in the granule treatment group. Overall, demographics between the two treatment groups was balanced. Most patients enrolled were male (39/71, 55% patients) and about half of the patients were white (36/71, 51% patients). The most common diagnosis for patients requiring iron transfusion was beta-thalassemia major (Beta-Thal. Major) (41/71, 58% patients). Overall, the median time from diagnosis to treatment was 2 years (range <1-13 years). The median dose of deferasirox administered in the DT treatment group was 20mg/kg/day (range 3-36 mg/kg/day) and the median dose of deferasirox administered in the granule treatment group was 15mg/kg/day (range 5-22 mg/kg/day).

Table 2. Study F2202 Demographics

Criterion	DT N=36 (n, %)	Granule N=35 (n, %)
Age (2<10 years)	32 (89%)	30 (86%)
Male	22 (61%)	17 (49%)
White	18 (50%)	18 (51%)
Asian	11 (31%)	11 (31%)
African American	5 (14%)	3 (9%)
Median Weight (kg) (range)	14 (10-42)	15 (10-56)
Median time since diagnosis (years)	2 (<1-8)	2 (<1-13)
Beta-Thal. Major	23 (64%)	18 (51%)
Sickle Cell Disease	4 (11%)	5 (14%)
Median Dose (mg/kg/day) (range)	20 (3-36)	15 (5-22)

Reviewer's table derived from F2202 study report (NDA 21882 supporting document 1134 letter date June 15, 2018 (received June 15, 2018))

Efficacy Results - Compliance

Compliance was assessed by the investigator and/or study personnel every 4 weeks during the 48 weeks of therapy and information provided by the subject and/or caregiver was captured. Compliance was calculated as the ratio of total count consumed to total count prescribed, where total count consumed was derived from cumulative dispensed, returned and lost/wasted counts over 24-weeks of treatment (i.e., assessed at Week 25 visit) and total count prescribed was cumulative prescribed count over 24-weeks of treatment (i.e., assessed at Week 25 visit) for the primary endpoint or 48 weeks for the secondary endpoint. Note that compliance at 24 weeks is only available for 61 of the planned 96 patients as of the November 16, 2017 data cut-off date for the F2202 study report. The formulas used by the sponsor to calculate compliance to deferasirox therapy are as follows.

- Overall compliance (%) using stick pack/tablet count: (total count consumed / total count prescribed)*100.
- Total count consumed: sum of counts dispensed - (sum of counts returned + lost/wasted).
- Total count prescribed: sum of counts prescribed calculated from the daily prescribed count multiplied by the duration (days).

Compliance appears to be similar between the two treatment groups at the 24-week primary endpoint (91% compliance in each treatment group) and slightly favors the DT treatment group (91% compliance) compared to the granule treatment group (88% compliance) at the 48-week secondary endpoint timepoint among the 61 patients for whom compliance data are available in the F2202 study report. The compliance to therapy is shown in the reviewer's table below.

Table 3. Study F2202 Compliance

Primary EP (24 weeks)	**DT N=32**	**Granule N=29**
Mean % (SD)	91% (11)	91% (17)
95% CI	87, 95	84, 97
Secondary EP (48 weeks)	**DT N=19**	**Granule N=17**
Mean % (SD)	91% (10)	88% (13)
95% CI	86, 96	81, 95

Reviewer's table derived from F2202 study report (NDA 21882 supporting document 1134 letter date June 15, 2018 (received June 15, 2018))

Reviewer comment: The calculation for compliance in the either treatment group assumes that the entire dose of deferasirox was consumed by the patient after the drug was dispersed into solution. Uncertainty as to the actual amounts of DT solution and granules taken may have some impact on results, i.e., level of serum ferritin and/or compliance. No statistical superiority comparison between treatment arms was performed by the sponsor. Only a descriptive analysis was performed on the primary endpoint. It is not expected that a statistically significant change in serum ferritin would be observed between the treatment groups, assuming similar compliance between the study drugs, because the active ingredient, i.e., deferasirox, is the same in each treatment arm. A larger study would need to be performed to observe any differences in serum ferritin between the two treatment arms.

Efficacy Results – Change in Serum Ferritin

Serum ferritin (SF) testing was performed at Screening Visits 1 and 2 (in the absence of infection) to assess the eligibility of the subject. The baseline SF value was defined as the average of the two measurements obtained during the

screening period. Thereafter SF testing was performed at weeks 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45 and end of treatment week 48 visits to evaluate the clinical benefit related to improved compliance of the new formulation. Note that the change in serum ferritin from baseline to week 24 is only available for 54 of the planned 96 patients as of the data cut-off date (November 16, 2017) in the F2202 study report.

At the 24-week primary endpoint timepoint and the 48-week secondary endpoint timepoint both treatment groups showed positive changes in serum ferritin compared to baseline. A positive change in SF implies an increase in body iron stores. At the 24 week timepoint the absolute change in serum ferritin was 349 ng/mL (95%CI = 84, 614 ng/mL) in the DT treatment group and 288 ng/mL (95%CI = 18, 558 ng/mL). At the 48 week timepoint the absolute change in serum ferritin was 452 ng/mL (95%CI = -146, 1050) in the DT treatment group and 202 ng/mL (95%CI = -326, 730) in the granule treatment group. The reviewer's table below shows the absolute change in serum ferritin level compared to baseline.

Table 4. F2202 Change in Serum Ferritin (Study F2202)

Time Point	DT N= 36	Granule N=35
Baseline (SD)	2068 (969)	1717 (501)
95%CI	1741, 2396	1545, 1889
24 weeks	**N=27**	**N=27**
Absolute Change (SD)	349 (670)	288 (682)
95%CI	84, 614	18, 558
48 weeks	**N=17**	**N=11**
Absolute Change (SD)	452 (1164)	202 (787)
95%CI	-146, 1050	-326, 730

Reviewer's table derived from F2202 study report (NDA 21882 supporting document 1134 letter date June 15, 2018 (received June 15, 2018))

Reviewer comment regarding the efficacy results from study F2202: At the 24 week timepoint the absolute change in SF was 349 ng/mL (95%CI = 84, 614 ng/mL) in the DT treatment group and 288 ng/mL (95%CI = 18, 558 ng/mL). At the 48 week timepoint the absolute change in SF was 452 ng/mL (95%CI = -146, 1050) in the DT treatment group and 202 ng/mL (95%CI = -326, 730) in the granule treatment group. Both treatment groups had increased serum ferritin at the two study timepoints (24 weeks and 48 weeks). However, the increase was less in the granule treatment group compared to the dispersible tablet treatment group. The relatively wide confidence intervals around the point estimates of SF change for each treatment group may be due to the small number of patients enrolled to date in study F2202. Nevertheless, the data suggests that deferasirox administered either as a DT or granule may decrease the rise of SF in pediatric patients at risk for iron overload due to increased requirement for red blood cell transfusions.

Overall Safety Results (Study F2202)

National Cancer Institute - Common Terminology Criteria for Adverse Events (CTCAE) v.4 were used to characterize and grade adverse events (AEs) and serious adverse events (SAEs) in study F2202. Data is available from 70 patients (1 patient was randomized but did not receive deferasirox treatment). The median exposure to deferasirox in the DT treatment group was 278 days (range 14-477 days) and 296 days (27-365 days) in the granule treatment group. SAEs were reported in 7 patients in the DT treatment group and 9 patients in the granule treatment group. Any AEs were reported in 36/36 (100%) patients in the DT treatment group and 31/34 (91%) patients in the granule treatment group. AEs reported in ≥ 10% patients in either treatment group include pyrexia (21/70, 30% patients), upper respiratory infection (17/70, 24% patients), serum aminotransferase increased (15/70, 21%) and increased urine protein/creatinine ratio 14/70, 20% patients). SAEs reported in ≥ 2 patients were sickle cell crisis in 2 patients each in the DT and granule treatment groups (4 total) and 2 reported cases of pyrexia in the granule treatment group compared to 1 in the DT treatment group (3 total). There were 16/36 (44%) patients in the DT treatment group and 17/34 (50%) patients in the granule treatment group that required a dose change due to an AE. AEs that were reported in ≥ 10% patients that resulted a change in deferasirox dosing in either treatment group were pyrexia (7/70, 10%) and urine protein/creatinine ratio increased (7/70, 10%). There were no deaths reported in the F2202 study report. The reviewer's table below summarizes the key safety data from the F2202 study report (data cut-off date November 16, 2017). Safety results of special interest, i.e., renal and hepatic function are discussed below in the sections Safety Results Renal Function (F2202 Report) and Safety Results Hepatic Function (F2202 Report).

Table 5. Summary of Key Safety Results (Study F2202)

Category	DT N=36 (n, %)	Granule N=34 (n, %)
Any AE	36 (100%)	31 (91%)
Any SAE	7 (19%)	9 (27%)
AE leading to d/c	2 (6%)	1 (3%)
AE leading to dosing change	16 (44%)	17 (50%)
Deaths	0 (0%)	0 (0%)

Reviewer's table derived from F2202 study report (NDA 21882 supporting document 1134 letter date June 15, 2018 (June 15, 2018))

Safety Results: Renal Function (Study F2202)

There were 0/36 patients in the DT treatment group and 0/34 patients in the granule treatment group who had creatinine clearance > 60 mL/min who

subsequently had a decrease creatinine clearance < 60 mL/min after deferasirox therapy as of the data cut-off date November 16, 2017.

Safety Results: Hepatic Function (Study F2202)

The sponsor's shift tables below show the proportion of patients with a change in serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT) and serum total bilirubin (TBili) from baseline for each treatment group. There were 7 patients in the DT treatment group and 8 patients in the granule treatment group that were reported with increased liver transaminases AST or ALT. Generally, a similar proportion of patients in each treatment group had an increase from baseline in ALT or AST, i.e., 35-50% of patients in each treatment group had an increase from baseline AST or ALT < ULN to > ULN-≤5xULN. No patients had a shift in AST or ALT from baseline < ULN to >10xULN. There were 53-61% of patients in each treatment group each treatment group who had an increase from baseline in TBili ≥ ULN to 2 x ULN and ≥ 2 x ULN. Generally, a similar proportion of patients in each treatment group had a TBILI increase from baseline > 2 x ULN (3/36 (8%)) patients in the DT treatment group and 4/34 (12%) patients in the granule treatment group). There were two patients in the DT treatment group and 0 patients in the granule treatment group with the AE increased serum total bilirubin defined as > 2mg/dL.

Table 6. Shift in AST (Study F2202)

	Baseline		Highest post-baseline value						
Treatment		n (%)	<=ULN n (%)	>ULN - <=5*ULN n (%)	>5*ULN- <=10*ULN n (%)	Notable range n (%)	>10*ULN n (%)	Extended range n (%)	Missing n (%)
DFX DT (N=36)	<=ULN	33 (91.7)	19 (57.6)	14 (42.4)	0	0	0	0	0
	>ULN - <=5*ULN	2 (5.6)	1 (50.0)	1 (50.0)	0	0	0	0	0
	>5*ULN - <=10*ULN	1 (2.8)	0	1 (100.0)	0	0	0	0	0
	>10*ULN	0	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0	0
	Total	36 (100.0)	20 (55.6)	16 (44.4)	0	0	0	0	0
DFX Granule (N=34)	<=ULN	30 (88.2)	13 (43.3)	15 (50.0)	0	1 (3.3)	0	1 (3.3)	0
	>ULN - <=5*ULN	4 (11.8)	0	4 (100.0)	0	0	0	0	0
	>5*ULN - <=10*ULN	0	0	0	0	0	0	0	0
	>10*ULN	0	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0	0
	Total	34 (100.0)	13 (38.2)	19 (55.9)	0	1 (2.9)	0	1 (2.9)	0

- ULN: Upper Limit of Normal
- Baseline is defined as the last non-missing value prior or on the day of first dose.
- Baseline percentage is based on N. percentage for highest post-Baseline value is based on Baseline n.
- Notable range: >5 x ULN and 2 x baseline.
- Extended range: >10×ULN and >2×baseline value.
- Within each classification, patients are only counted in the highest category.

Sponsor's table from F2202 study report (NDA 21882 supporting document 1134 letter date June 15, 2018 (received June 15, 2018))

Table 7. Shift in ALT (F2202)

	Baseline		Highest post-baseline value						
Treatment		n (%)	<=ULN n (%)	>ULN - <=5*ULN n (%)	>5*ULN- <=10*ULN n (%)	Notable range n (%)	>10*ULN n (%)	Extended range n (%)	Missing n (%)
DFX DT (N=36)	<=ULN	31 (86.1)	17 (54.8)	14 (45.2)	0	0	0	0	0
	>ULN - <=5*ULN	4 (11.1)	1 (25.0)	3 (75.0)	0	0	0	0	0
	>5*ULN - <=10*ULN	1 (2.8)	0	0	1 (100.0)	0	0	0	0
	>10*ULN	0	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0	0
	Total	36 (100.0)	18 (50.0)	17 (47.2)	1 (2.8)	0	0	0	0
DFX Granule (N=34)	<=ULN	28 (82.4)	14 (50.0)	10 (35.7)	0	4 (14.3)	0	0	0
	>ULN - <=5*ULN	6 (17.6)	0	5 (83.3)	0	1 (16.7)	0	0	0
	>5*ULN - <=10*ULN	0	0	0	0	0	0	0	0
	>10*ULN	0	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0	0
	Total	34 (100.0)	14 (41.2)	15 (44.1)	0	5 (14.7)	0	0	0

- ULN: Upper Limit of Normal
- Baseline is defined as the last non-missing value prior or on the day of first dose.
- Baseline percentage is based on N. percentage for highest post-Baseline value is based on Baseline n.
- Notable range: >5 x ULN and 2 x baseline.
- Extended range: >10×ULN and >2×baseline value.
- Within each classification, patients are only counted in the highest category.

Sponsor's table from F2202 study report (NDA 21882 supporting document 1134 letter date June 15, 2018 (received June 15, 2018))

Table 8. Shift in TBili (F2202)

	Baseline		Highest post-baseline value			
Treatment		n (%)	< ULN n (%)	>= ULN - 2 x ULN n (%)	> 2 x ULN n (%)	Missing n (%)
DFX DT (N=36)	< ULN	28 (77.8)	14 (50.0)	13 (46.4)	1 (3.6)	0
	>= ULN - 2x ULN	8 (22.2)	0	6 (75.0)	2 (25.0)	0
	> 2x ULN	0	0	0	0	0
	Missing	0	0	0	0	0
	Total	36 (100.0)	14 (38.9)	19 (52.8)	3 (8.3)	0
DFX Granule (N=34)	< ULN	25 (73.5)	15 (60.0)	9 (36.0)	1 (4.0)	0
	>= ULN - 2x ULN	8 (23.5)	0	5 (62.5)	3 (37.5)	0
	> 2x ULN	1 (2.9)	0	0	1 (100.0)	0
	Missing	0	0	0	0	0
	Total	34 (100.0)	15 (44.1)	14 (41.2)	5 (14.7)	0

Sponsor's table from Response to Information Request regarding F2202 study report (NDA 21882 supporting document 1140 letter date July 18, 2018 (received July 18, 2018)

Safety Results: Cardiac (Study F2202 Report)

A 12 lead electrocardiogram (ECG) and echocardiography were performed at Visit 1 and at the end of therapy (EOT) and was completed by 55 patients. Of the 71 patients included in the F2202 study interim analysis there were five patients with baseline ECG abnormalities and two patients with missing baseline ECG data (7/55, 13%). However, no ECG/echocardiography data was provided by the sponsor in the interim analysis of study F2202 (submitted under NDA 21882

Supporting Document 1134, NDA 206910 Supporting Document 440 and NDA 207968 Supporting Document 112 letter date June 15, 2018 (received June 15, 2018)) because this data was considered to be preliminary.

Reviewer comment regarding cardiac safety findings study F2202: The sponsor proposes to evaluate the cardiac safety data (ECG and echocardiography) with the submission of the F2202 completed study report (CSR). The sponsor's proposal is acceptable because the current available data appears to be preliminary and a relatively high number of patients appear to have baseline cardiac (ECG or echocardiography) abnormalities or missing data. A larger number of patients with interpretable ECG/echocardiography data would enhance the safety database of deferasirox.

Safety Results: Ophthalmology (Study F2202 Report)

In study F2202 specific ophthalmologic safety evaluations were to be conducted because of concerns raised in the original adult studies for deferasirox. The ophthalmologic adverse reactions included lens opacities, cataracts, elevations in intraocular pressure, and retinal disorders that were reported at a frequency of less than 1% among subjects treated with deferasirox. Ophthalmologic examination included distance visual acuity testing, applanation tonometry, lens photography and wide angle fundus photography of the retina and optic nerve. In the study F2202 interim analysis (submitted under NDA 21882 Supporting Document 1134, NDA 206910 Supporting Document 440 and NDA 207968 Supporting Document 112 letter date June 15, 2018 (received June 15, 2018)) there were 56 patients, i.e., 29 patients in the dispersible treatment (DT) arm and 27 patients in the granule treatment arm, who completed all ocular examination tests at baseline. Among these there were 45 patients, i.e., 25 patients in the DT arm and 20 patients in the granule treatment arm who completed all ocular examination tests at baseline and at least one post baseline assessment at any time during the treatment period. There were only 23 patients, i.e., 13 patients in the DT arm and 10 patients in the granule treatment arm who completed all ophthalmologic examination tests as per protocol (ophthalmologic examinations performed at baseline, after 24 weeks of therapy and at the end of therapy).

Reviewer comment regarding the ophthalmology safety findings in study F2202: The data submitted were also reviewed by Dr. Wiley Chambers (Deputy Director in the Division of Transplant and Ophthalmology). Dr. Chambers states that the ophthalmic portion of the submission is problematic. In addition to the low numbers, there are a number of observations listed as clinically insignificant abnormalities without describing the abnormality (case report form did not ask for it if it was clinically insignificant) or with values which are not clinically insignificant (raises questions about the insignificant assessments without values). There are 5 baseline intraocular pressure measurements listed as normal, without giving the values. There are some 2 years old children who seem to have been able to read an eye chart and various other oddities. (See personal e-mail

communication from Dr. Chambers dated October 30, 2018 in Appendix 3 in this review). I agree with Dr. Chambers' review of the interim analysis ophthalmology safety data from study F2202. Interpretation of this data is difficult. The sponsor should submit updated ophthalmology safety data with the submission of the complete study report (CSR) for study F2202.

Reviewer comment regarding the overall safety findings in study F2202: Overall, among 70 patients for whom data is available in the F2202 study report the safety results including the types and severity of AEs and SAEs are similar to the reported AEs in the deferasirox (Exjade) label approved February 16, 2018 under NDA 21882 and the deferasirox (Jadenu Sprinkle) label approved February 16, 2018 under NDA 207968. Also, generally, a similar proportion of patients in each treatment group had an increase from baseline in ALT or AST, i.e., 35-50% of patients in each treatment group had an increase from baseline AST or ALT < ULN to > ULN-≤5xULN. There were 53-61% of patients in each treatment group each treatment group who had an increase from baseline in TBili ≥ ULN to 2 x ULN and ≥ 2 x ULN. Generally, a similar proportion of patients in each treatment group had a TBILI increase from baseline > 2 x upper limit of normal (3/36 (8%)) patients in the DT treatment group and 4/34 (12%) patients in the granule treatment group).

The sponsor has demonstrated in study F2202 for deferasirox administered as a DT or granule formulation that the granule tablet formulation has similar compliance compared to the DT formulation. The granule formulation also had comparable effects on serum ferritin change from baseline at 24 and 48 weeks. Deferasirox administered either as a DT or granule appears to be able to slow down the rise of SF. Also, generally, the safety of the granule formulation of deferasirox appeared comparable to that of the DT formulation of deferasirox in pediatric patients based on available interim data from study F2202.

Sponsor Proposed Exjade, Jadenu and Jadenu Sprinkle Labeling Changes

The sponsor proposes the following labeling change to all three deferasirox product labels based on the results of study F2202, i.e., Exjade (NDA 21882), Jadenu (NDA 206910) and Jadenu Sprinkle (NDA 207968).

- Under section 8.4 Pediatric Use the sponsor proposes the following wording addition (underlined format).
  - (b) (4)

(b) (4)

- *Reviewer comment: The sponsor's proposed wording that compliance of patients who were treated with either formulation of deferasirox, (b) (4) is promotional and should be deleted. The wording, (b) (4) , should be deleted for readability. The sponsor's proposed wording was also reviewed by Dr. Robert Nguyen (Regulatory Review Officer in the Office of Prescription Drug Promotion (OPDP) final signature date November 27, 2018), Dr. Elizabeth L. Durmowicz (Medical Officer in the Division of Pediatric and Maternal Health (DPMH) final signature date November 14, 2018 and Dr. Nicole Garrison (Safety Evaluator in the Division of Medication Error Prevention and Analysis (DMEPA) final signature date October 16, 2018) I agree with the reviews and recommendations by Dr. Nguyen, Dr. Durmowicz and Dr. Garrison. Also, the sponsor's analyses of the efficacy data (serum ferritin levels and compliance) from study FF202 is considered a post-hoc analysis. The results from the analysis are considered inconclusive. In order for the sponsor to claim similarity in labeling, an equivalence study with a prespecified margin of equivalence and planned sample size according to the margin need to be conducted. The FDA proposed revised wording for the paragraph is shown below and should be forwarded to the sponsor. The paragraph should read as follows (wording to be added is in double underlined format).*

  - *A trial conducted in treatment naïve pediatric patients, ages 2 years < 18 years with transfusional iron overload did not include a sufficient number of patients to provide additional meaningful information about the safety or compliance of the deferasirox oral tablets for suspension dosage form (Exjade) compared to the deferasirox granules dosage form (Jadenu Sprinkle).*

    Overall safety profiles were also similar between the two formulations.

III. Conclusions

In NDA 21882 supporting document 1123 letter date March 30, 2018 (received March 30, 2018) the sponsor submitted a report for study CICL670F2202 (F2202), titled "A Randomized, Open-Label, Multicenter, Two Arm, Phase 2 Study To Evaluate Treatment Compliance, Efficacy And Safety Of An Improved Deferasirox Formulation (Granules) In Pediatric Patients With Iron Overload", and requests pediatric exclusivity determination for deferasirox. The most recent version of the F2202 protocol (version 5 dated December 6, 2017) was submitted under IND 58554 supporting document 869 letter date January 5, 2018 (received

January 5, 2018). The sponsor states, and I agree, that the information from study F2202 and the request for pediatric exclusivity determination for deferasirox extends to all the approved formulations of deferasirox, i.e., Exjade® tablets for Oral suspension (accelerated approval for marketing granted under NDA 21882), Jadenu® Tablets, for oral use (accelerated approval granted under NDA 206910) and Jadenu® Sprinkle granules for oral use (accelerated approval for marketing granted under NDA 207968). The sponsor's request for determination of pediatric exclusivity for deferasirox (under NDAs 21882, 206910 and NDA 207968) was discussed with the Pediatric Exclusivity Board on October 24, 2018.

Regarding the number of patients to be studied, the WR stated, "A sufficient number of patients must be enrolled to ensure that the study is adequately powered to detect a statistically significant and clinically relevant improvement in compliance and difference in change in serum ferritin from baseline to 48 weeks between the two treatment arms." Patients enrolled in the study were also to be ICT-naive. As of the data cut-off (November 16, 2017), 206/216 subjects were enrolled in study F2202 which included includes 90/96 ICT naive subjects and 116/120 ICT pre-treated subjects. Although the trial enrolled iron chelation therapy (ICT) pre-treated subjects and ICT naive subjects, the data submitted in the study report for study F2202 focuses on all randomized ICT naive subjects, who have 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. The efficacy analysis set includes 71/96 patients and the safety set includes 70/96 ICT-naïve patients.

Compliance appears to be similar between the two treatment groups (DT and granules) at the 24-week primary endpoint (91% compliance in each treatment group) and slightly favors the DT treatment group (91% compliance) compared to the granule treatment group (88% compliance) at the 48-week secondary endpoint timepoint among the 61 patients for whom compliance data are available in the F2202 study report. At the 24 week timepoint the absolute change in serum ferritin was 349 ng/mL (95%CI = 84, 614 ng/mL) in the DT treatment group and 288 ng/mL (95%CI = 18, 558 ng/mL). At the 48 week timepoint the absolute change in serum ferritin was 452 ng/mL (95%CI = -146, 1050) in the DT treatment group and 202 ng/mL (95%CI = -326, 730) in the granule treatment group. The small changes in serum ferritin are of unclear clinical significance which may be due to the small number of patients enrolled in the study to date. Nevertheless, deferasirox administered either as a DT or granule appears to be able to slow down the rise of SF. Given the small numbers of patients for whom data is available in the study report conclusions regarding differences in serum ferritin from baseline to 24 or 48 weeks based on the type of therapy, i.e., DT or granules, are difficult to make.

Overall, among 70 patients for whom data is available in the F2202 study report the safety results including the types and severity of AEs and SAEs are similar to that stated in the deferasirox (Exjade) label approved February 16, 2018 under

NDA 21882 and the deferasirox (Jadenu Sprinkle) label approved February 16, 2018 under NDA 207968. Any AEs were reported in 36/36 (100%) patients in the DT treatment group and 31/34 (91%) patients in the granule treatment group. AEs reported in ≥ 10% patients in either treatment group include pyrexia (21/70, 30% patients), upper respiratory infection (17/70, 24% patients), serum aminotransferase increased (15/70, 21%) and increased urine protein/creatinine ratio 14/70, 20% patients). SAEs reported in ≥ 2 patients were sickle cell crisis in 2 patients each in the DT and granule treatment groups (4 total) and 2 reported cases of pyrexia in the granule treatment group compared to 1 in the DT treatment group (3 total). There were 0/36 patient in the DT treatment group and 0/34 patients in the granule treatment group who had creatinine clearance > 60 mL/min who subsequently had a decrease creatinine clearance < 60 mL/min after deferasirox therapy as of the data cut-off date November 16, 2017. Generally, a similar proportion of patients in each treatment group had an increase from baseline in ALT or AST, i.e., 35-50% of patients in each treatment group had an increase from baseline AST or ALT < ULN to > ULN-≤5xULN. No patients had a shift in AST or ALT from baseline < ULN to >10xULN. There were two patients in the DT treatment group and 0 patients in the granule treatment group with the AE increased serum total bilirubin defined as > 2mg/dL. The sponsor should submit a shift table for that shows the proportion of patients with normal serum total bilirubin who may have had an increased serum total bilirubin > 2xULN after treatment with DT or granules with their final report for study F2202.

The sponsor proposes to evaluate the cardiac safety data (ECG and echocardiography) with the submission of the F2202 completed study report (CSR). The sponsor's proposal is acceptable because a larger number of patients with interpretable ECG/echocardiography data would enhance the safety database of deferasirox. Also, interpretation of the ophthalmologic safety data from the interim analysis of study F2202 is difficult. The sponsor should submit updated ophthalmology safety data with the submission of the complete study report (CSR) for study F2202.

IV. Recommendations

The following recommendations should be forwarded to the sponsor.

- You should complete enrollment of all 96 ICT-naïve patients into study F2202.
- The following labeling change should be incorporated in the product labels under section 8.4 Pediatric Use (FDA proposed wording to be added is in underlined format).

    - <u>A trial conducted in treatment naïve pediatric patients, ages 2 years < 18 years with transfusional iron overload did not include a sufficient number of patients to provide additional meaningful</u>

information about the safety or compliance of the deferasirox oral tablets for suspension dosage form (Exjade) compared to the deferasirox granules dosage form (Jadenu Sprinkle).

Overall safety profiles were also similar between the two formulations.

APPEARS THIS WAY ON ORIGINAL

Appendix 1. Synopsis of Amended Protocol F2202 (Version 05 dated December 6, 2017)

Protocol number	CICL670F2202
Title	A randomized, open-label, multicenter, two arm, phase II study to evaluate treatment compliance, efficacy and safety of an improved deferasirox formulation (granules) in pediatric patients with iron overload
Brief title	Study to evaluate treatment compliance, efficacy and safety of an improved deferasirox formulation (granules) in pediatric patients (2-<18 years old) with iron overload
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of the present study is to: ▪ assess the compliance of the granule and the dispersible tablet (DT) formulations in pediatric patients with iron overload over 24 weeks and 48 weeks of treatment, using stick pack/tablet count and pre-dose pharmacokinetic (PK) concentrations and a PRO questionnaire. ▪ assess the clinical benefit due to improved compliance of the new formulation by measurements of serum ferritin levels for both formulations, after 24 and 48 weeks of treatment. ▪ assess Patient / Observer Reported Outcomes (PRO/ObsRO) on palatability and treatment satisfaction ▪ assess the safety of both formulations ▪ examine the pre- and post-dose concentrations of both formulations using sparse PK sampling ▪ explore exposure-response (PK/PD) relationships for measures of safety and effectiveness ▪ assess long term safety of granules formulation via an optional extension phase consisting of up to 5 years for those who complete 48 weeks of core treatment phase and choose to continue in the extension phase
Primary Objective(s)	To evaluate patient compliance (using stick pack or tablet counts) and change in serum ferritin over time for both formulations of deferasirox, i.e., granules and dispersible tablet (DT) in iron chelation therapy (ICT) naïve patients in the first 24 weeks of treatment during the core phase.
Secondary Objectives	▪ To evaluate both formulations on patient compliance (using stick pack or tablet counts) and change in serum ferritin in ICT naïve patients, after 48 weeks of treatment ▪ To evaluate both formulations on change in serum ferritin in ICT naïve and pretreated patients, after 24 weeks and 48 weeks of treatment ▪ To evaluate both formulations on patient satisfaction and palatability using PRO/ObsRO questionnaires ▪ To evaluate both formulations on overall safety ▪ To evaluate compliance using a daily PRO/ObsRO questionnaire ▪ To evaluate pre-dose PK data to support the assessment of compliance ▪ To obtain pre- and post-dose concentrations to explore exposure-response relationships ▪ To assess long-term safety of the granules formulation during the optional extension phase for patients who choose to continue

Study design	This is a randomized, open-label, multicenter, two arm, phase II study to evaluate treatment compliance and change in serum ferritin of a deferasirox granule formulation and a deferasirox DT formulation in children and adolescents aged ≥ 2 and < 18 years at enrollment with any transfusion-dependent anemia requiring chelation therapy due to iron overload, to demonstrate the effect of improved compliance on iron burden. Randomization will be stratified by age groups (2 to <10 years, 10 to <18 years) and prior iron chelation therapy (Yes/ No). There will be two study phases which include a 1 year core phase where patients will be randomized to a 48 week treatment period to either Deferasirox DT or granules, and an optional extension phase where all patients will receive the granules up to 5 years from entering extension phase. Patients who demonstrated benefit to granules or DT in the core phase, and/or express the wish to continue in the optional extension phase on granules, will be offered this possibility until there is local access to the new formulation (granules or FCT) or up to 5 years from entering extension phase, whichever occurs first. One interim analysis has been added to allow for early analysis of the core phase data if requested by the health authority. All patients randomized in the study and who have completed a minimum of 12 weeks of treatment exposure or discontinued from treatment core phase at the time of the cutoff date will be included in the interim analysis.
Population	Up to 216 naïve and pre-treated (96 ICT naïve and up to 120 pre-treated) male and female children and adolescents aged ≥ 2 and < 18 years at enrollment with any transfusion-dependent anemia requiring chelation therapy due to iron overload, and a treatment goal to reduce iron burden will be included in this study. At least 96 (48 per treatment arm) patients should be iron chelation naïve. The optional extension phase will give the patients who have participated and completed the 48 weeks core treatment phase as per protocol, the possibility to extend treatment with granules for a maximum of 5 years after completing the core treatment phase or until there is local access to new formulation (granules or FCT), whichever occurs first. All patients who choose to continue in the extension phase will receive granules during the optional extension phase. There will be two study phases which include a 1 year core phase where patients will be randomized to a 48 week treatment period to either Deferasirox DT or granules, and an optional extension phase where all patients will receive the granules up to 5 years from entering extension phase. Patients who demonstrated benefit to granules or DT in the core phase, and/or express the wish to continue in the optional extension phase on granules, will be offered this possibility until there is local access to the new formulation (granules or FCT) or up to 5 years from entering extension phase, whichever occurs first.
Inclusion criteria	• Written informed consent/assent before any study-specific procedures. Consent will be obtained from patients, parent(s) or legal guardians. Investigators will also obtain consent/assent of patients according to local guidelines. • Male and female children and adolescents aged ≥ 2 and < 18 years.* [France: Male and female children and adolescents aged ≥ 2 and < 18 years, however children aged ≥ 2 and ≤ 6 years can be enrolled only when deferoxamine treatment is contraindicated or inadequate in these patients as per investigator decision] *Applicable to core phase only. Once in the core phase patients can turn 18 years and still be considered eligible, also for participation in the optional extension phase. • Any transfusion-dependent anemia associated with iron overload requiring iron chelation therapy and with a history of transfusion of approximately 20 PRBC units, and a treatment goal of reduction, not maintenance of iron burden as measured by serum ferritin. • Serum ferritin > 1000 ng/mL, measured at screening Visit 1 and screening Visit 2 (the mean value will be used for eligibility criteria).

	• Completion of core phase per protocol (For the optional extension phase criteria only).
Exclusion criteria	• Creatinine clearance below the contraindication limit in the locally approved prescribing information. Creatinine clearance will be estimated from serum creatinine (using the Schwartz formula) at screening Visit 1 or screening Visit 2. • Serum creatinine > 1.5 xULN at screening Visit 1 or screening Visit 2. • ALT or AST >3.0 x ULN at screening visit 1 or screening visit 2. • Direct (conjugated) bilirubin >2 x ULN at screening visit 1 or screening visit 2. • (Criterion no longer applicable, removed as part of Amendment 1): ~~Prior iron chelation therapy~~ • Liver disease with severity of Child-Pugh class B or C. • Significant proteinuria as indicated by a urinary protein/creatinine ratio >0.5 mg/mg in a second morning urine sample at screening Visit 1 or screening Visit 2. • Patients with significant impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral deferasirox (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection). • Clinical or laboratory evidence of active Hepatitis B or Hepatitis C (HBsAg in the absence of HBsAb OR HCV Ab positive with HCV RNA positive). • Patients with psychiatric or addictive disorders which prevent them from giving their informed consent/assent or undergoing any of the treatment options or patients unwilling or unable to comply with the protocol (including use of electronic devices for ePRO). • Local access to new formulation (granules or FCT) is available for the patient (For the optional extension phase criteria only).
Investigational and reference therapy	• Patients will be randomized to either Deferasirox granules or Deferasirox DT (Exjade) in the core phase. • All patients who choose to continue in the extension phase will receive deferasirox granules in the extension phase.
Efficacy assessments	The co-primary efficacy endpoints assessed during the core phase will be: • Compliance measured by stick pack/tablet count over 24 weeks of treatment (i.e. assessed at week 25 visit). • Change from baseline in serum ferritin after 24 weeks of treatment (i.e. Serum Ferritin at week 25 visit).
Primary endpoint assessments	• Compliance will be measured by stick pack/tablet count over 24 weeks of treatment (i.e. assessed at week 25 visit): it will be performed by study personnel every 4 weeks (weeks 5, 9, 13, 17, 21, 25 and EOT(core)/777 visits) during the core phase based on the amount of medication dispensed, returned and reported as lost/wasted by the patient / caregiver • Serum ferritin test will be performed at Screening Visits 1 and 2 and every 4 weeks from week 5 till after 24 weeks of treatment (i.e. assessed at week 25 visit)..
Secondary endpoint assessments	Core phase: • Compliance will be measured by stick pack/tablet count over 48 weeks of treatment: it will be performed by study personnel every 4 weeks (weeks 5, 9, 13, 17, 21, 25 29, 33, 37, 41, 45, and EOT(core)/777 visits) during the core phase based on the amount of medication dispensed, returned and reported as lost/wasted by the patient / caregiver • Serum ferritin test will be performed at Screening Visits 1 and 2 and every 4 weeks from week 5 till end of treatment visit. • The study will include the use of a Satisfaction with Iron Chelation Therapy questionnaire, a Palatability questionnaire and a compliance diary to evaluate

	both formulations on these patient / observer reported outcomes. • Safety will be monitored by assessing the following parameters: • Hematology, chemistry (including renal and hepatic parameters), urinalysis • Adverse events; including renal toxicity (including renal failure), hepatic toxicity (including hepatic failure) and gastrointestinal hemorrhage, which will be actively monitored until symptom resolution or until the condition stabilizes • Vital signs • Physical examinations • Ocular examinations • Auditory examinations • Cardiac examinations (ECG and echocardiogram) • Growth parameters and development parameters • Deferasirox concentrations will be measured in plasma at predefined time points on all patients. [Egypt: PK samples will not be collected due to restriction on sample exportation] • Pharmacokinetic samples collected by sparse PK sampling in all patients [Egypt: PK samples will not be collected] will be analyzed using modeling approaches to explore PK/PD (safety and efficacy) relationships. **Optional Extension phase:** • Long term safety of granules in the optional extension phase: • Overall safety, as measured by frequency and severity of adverse events (including active monitoring for renal toxicity; including renal failure, hepatic toxicity; including hepatic failure, and gastrointestinal hemorrhage), and changes in laboratory values from baseline (serum creatinine, creatinine clearance, ALT, AST, RBC and WBC). In addition, vital signs, physical, ophthalmological, audiometric, and growth and development evaluations will be assessed.
Other assessments	Daily questionnaire on study treatment compliance completed through core phase only.
Data analysis	Analysis sets: The Full Analysis Set 1 (FAS-1) comprises all ICT naïve patients to whom study treatment has been assigned by randomization. The Full Analysis Set 2 (FAS-2) comprises all ICT pre-treated patients to whom study treatment has been assigned by randomization. The Full Analysis Set 3 (FAS-3) comprises all ICT pre-treated and naïve patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment and stratification factors they have been assigned to during the randomization procedure. The Safety Set 1 includes all ICT naïve patients who received at least one dose of study medication. The Safety Set 2 includes all ICT pre-treated patients who received at least one dose of study medication. The Safety Set 3 includes all ICT pre-treated and naïve patients who received at least one dose of study medication. The Safety Set 4 will consist of all patients who received at least one dose of granules formulation during the core or extension phase. Patients will be analyzed according to the study treatment they actually received. The Per Protocol Set consists of all ICT naïve patients from the FAS-1 without any major protocol deviation. The major protocol deviations that will lead to exclusion of patients from the PPS will be detailed in the RAP. The Pharmacokinetic Analysis Set (PAS) consists of all patients who have at least one evaluable pre or post-dose PK concentration (deferasirox). More details are provided in Section 10.1.4. Statistical Analyses: Primary efficacy endpoints: All analyses for the primary objective will be

	both formulations on these patient / observer reported outcomes. • Safety will be monitored by assessing the following parameters: • Hematology, chemistry (including renal and hepatic parameters), urinalysis • Adverse events; including renal toxicity (including renal failure), hepatic toxicity (including hepatic failure) and gastrointestinal hemorrhage, which will be actively monitored until symptom resolution or until the condition stabilizes • Vital signs • Physical examinations • Ocular examinations • Auditory examinations • Cardiac examinations (ECG and echocardiogram) • Growth parameters and development parameters • Deferasirox concentrations will be measured in plasma at predefined time points on all patients. [Egypt: PK samples will not be collected due to restriction on sample exportation] • Pharmacokinetic samples collected by sparse PK sampling in all patients [Egypt: PK samples will not be collected] will be analyzed using modeling approaches to explore PK/PD (safety and efficacy) relationships. **Optional Extension phase:** • Long term safety of granules in the optional extension phase: • Overall safety, as measured by frequency and severity of adverse events (including active monitoring for renal toxicity; including renal failure, hepatic toxicity; including hepatic failure, and gastrointestinal hemorrhage), and changes in laboratory values from baseline (serum creatinine, creatinine clearance, ALT, AST, RBC and WBC). In addition, vital signs, physical, ophthalmological, audiometric, and growth and development evaluations will be assessed.
Other assessments	Daily questionnaire on study treatment compliance completed through core phase only.
Data analysis	Analysis sets: The Full Analysis Set 1 (FAS-1) comprises all ICT naïve patients to whom study treatment has been assigned by randomization. The Full Analysis Set 2 (FAS-2) comprises all ICT pre-treated patients to whom study treatment has been assigned by randomization. The Full Analysis Set 3 (FAS-3) comprises all ICT pre-treated and naïve patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment and stratification factors they have been assigned to during the randomization procedure. The Safety Set 1 includes all ICT naïve patients who received at least one dose of study medication. The Safety Set 2 includes all ICT pre-treated patients who received at least one dose of study medication. The Safety Set 3 includes all ICT pre-treated and naïve patients who received at least one dose of study medication. The Safety Set 4 will consist of all patients who received at least one dose of granules formulation during the core or extension phase. Patients will be analyzed according to the study treatment they actually received. The Per Protocol Set consists of all ICT naïve patients from the FAS-1 without any major protocol deviation. The major protocol deviations that will lead to exclusion of patients from the PPS will be detailed in the RAP. The Pharmacokinetic Analysis Set (PAS) consists of all patients who have at least one evaluable pre or post-dose PK concentration (deferasirox). More details are provided in Section 10.1.4. Statistical Analyses: Primary efficacy endpoints: All analyses for the primary objective will be

	performed based on core period and on the FAS-1 and presented by treatment group: deferasirox DT and deferasirox granule formulation. The co-primary efficacy variables are: • Compliance measured by stick pack /tablet count based on amount of medication dispensed, returned and reported as lost/wasted by the patient or caregiver over 24 weeks of treatment (i.e. assessed at week 25 visit). Compliance will be calculated as the ratio of total count consumed to total count prescribed, where • total count consumed is derived from cumulative dispensed, returned and lost/wasted counts over 24 weeks of treatment (i.e. assessed at week 25 visit); • total count prescribed is cumulative prescribed count over 24 weeks of treatment (i.e. assessed at week 25 visit). • Change from baseline in serum ferritin after 24 weeks of treatment (i.e. serum ferritin assessment at week 25 visit). The primary efficacy analysis will be the comparison of means between the two treatment arms of change from baseline after 24 weeks of treatment in SF and mean relative consumed stick pack /tablet count over 24 weeks of treatment. Analysis of covariance (ANCOVA) will be performed for comparison between treatment groups at a one-sided 5% level of significance. The ANCOVA model for compliance endpoint will include treatment group and age group (2 to<10 years, 10 to <18 years), as factors. The model for serum ferritin endpoint will also include the serum ferritin value at baseline as covariate. The trial will be claimed successful if the superiority of granule formulation relative to DT formulation could be demonstrated with regard to both endpoints. Therefore, no adjustment of the type I error (alpha) is required. Sample size calculation: The primary objective is to evaluate patient compliance (using stick packs or tablets counts) and change in serum ferritin (SF) over time for both formulations of deferasirox in pediatric ICT naïve patients with iron overload after 24 weeks of treatment. The sample size was calculated to show superiority of the granule formulation relative to DT formulation with regard to both co-primary endpoints. The assumptions made for this study were as follows: • For serum ferritin: An expected improvement between both formulations in SF change from baseline after 24 weeks 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 after 24 weeks of treatment. • For compliance over 24 weeks of treatment using stick packs or tablets counts: An expected improvement between both formulations 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), [ICL670A2204] (24) and [ICL670A2214] (14). The sample size driven by the calculation for serum ferritin, has been determined to obtain 76% power at 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 serum ferritin, assuming a dropout rate of 5%. A sample size of 48 in each group will have 76% power to detect a difference in means of 400.0 ng/mL assuming that the common SD is 800.0 ng/mL using a two group t-test with a 0.050 one-sided significance level. With 48 patients per arm, the power to detect a 10% difference in mean compliance is about 84%. In addition, the clinical trial will enroll patients previously treated with iron chelation. Considering that a direct comparison of granule and DT formulations in terms of efficacy is not foreseen in previously chelated patients, the required sample size is not based on power calculations as usual. The selection of number of patients is based on the precision in the estimate of SF change at 48 weeks of treatment and

on practical considerations.
A maximum of 120 patients (60 patients will be in each formulation group) previously chelated patients will be enrolled. Sixty patients will provide an estimate of SF change with precision (half-width of 95% confidence interval) equal to 303.6.
The table below lists the precisions in the estimates of SF change for different numbers of patients using the estimated SD obtained from the CICL670A0107 study results in pediatric patients treated with Exjade on ≥25 mg/kg/day at week 48 of treatment.
Precision in the estimate of the serum ferritin change

Number of patients	Half-width of 95% confidence interval in the estimate of the SF change
40	371.8
45	350.6
50	332.6
55	317.1
60	303.6

The total required sample size for this clinical trial is up to 108 patients for each treatment group (up to 216 patients in total), including 48 iron chelation naive patients per group (96 patients in total).

Safety: The assessment of safety will be based mainly on the frequency and severity of AEs and changes in laboratory values. Other safety data (e.g., ECGs, vital signs, echocardiogram, ocular, auditory examinations) will also be summarized. For all safety analyses, the safety set will be used.

Pharmacokinetics:
Pre- and post-dose concentrations will be summarized descriptively and graphically presented.
The analyses will be based on the PAS.

To explore PKPD relationship:
Serum ferritin change from baseline will be fitted by a linear mixed effect model with log- transformed matching pre-dose concentrations as covariates and subject as random effect.
Serum creatinine change from baseline, serum creatinine clearance change from baseline and urine protein creatinine ratio change from baseline will be fitted by a linear mixed effect model with log-transformed matching pre-dose concentrations and post-dose concentrations respectively as covariates and subject as random effect. Incidence of notable serum creatinine events will be analyzed by a logistic regression fitted by GEE methods as appropriate including matching log-transformed pre-dose concentrations and post-dose concentrations respectively. Incidence of notable serum creatinine clearance events will be analyzed by a logistic regression fitted by GEE methods as appropriate including matching log-transformed pre-dose concentrations post-dose concentrations respectively.
For all statistical models other covariates such as demographic characteristics may be included if appropriate.
All analyses will be based on the Safety Set or FAS of the core phase.

Interim analysis:
All the analyses included in the interim analysis will be descriptive. Testing of hypotheses will not be performed and no decisions regarding the future course of the trial is anticipated at the time of the IA and the trial will continue. Therefore adjustment for multiplicity is not performed. Descriptive statistics will be provided by treatment arm on the primary endpoints (i.e. change from baseline in serum ferritin and compliance measured by stick pack /tablet count) and key safety data.

Key words	New formulation, deferasirox, chelation, iron overload, compliance, satisfaction, palatability, PRO, PK, safety, PK/PD

Amended protocol F2202 (version 05 dated December 6, 2017) from NDA 21882 supporting document 1123 letter date March 30, 2018 (received March 30, 2018)

Appendix 2. Summary of Key Changes in Study F2202

Design element	Version 0 September 2, 2014	Version 2 February 6, 2015	Version 5 December 6, 2017
Objective	Evaluate patient compliance (stick pack or tablet counts)	Evaluate patient compliance (stick pack or tablet counts) and change in serum ferritin	Evaluate patient compliance (stick pack or tablet counts) and change in serum ferritin
Primary endpoint	48 weeks	48 weeks	24 weeks
Total number of patients to be enrolled	80	216	206
Key Enrollment, (n=number to be enrolled)	Treatment naïve and previously treated (80)	Treatment naïve (96) and previously treated (120)	Treatment naïve (71)* and previously treated (135)
Stratification	2 to <10 years 10 to <18 years	2 to <10 years 10 to <18 years	2 to <10 years 10 to <18 years

Reviewer's table

Appendix 3. Personal E-mail Communication from Dr. Chambers Dated October 30, 2018

From: Chambers, Wiley A
Sent: Tuesday, October 30, 2018 1:38 AM
To: Robie Suh, Kathy M
Cc: Dmytrijuk, Andrew; Gwathmey, Michael; Farrell, Ann T; Deisseroth, Albert; Reaman, Gregory; Yao, Lynne P; Boyd, William M
Subject: RE: NDA 21882 Exjade -- WR Exclusivity Determination -- ocular examinations

The ophthalmic portion of the submission is problematic. In addition to the low numbers, there are a number of observations listed as clinically insignificant abnormalities without describing the abnormality (case report form did not ask for it if it was clinically insignificant) or with values which are not clinically insignificant (raises questions about the insignificant assessments without values). There are 5 baseline intraocular pressure measurements listed as normal, without giving the values. There are some 2 years old children who seem to have been able to read an eye chart and various other oddities.

I would not support that this is an adequate assessment of ocular safety as presently submitted.

Wiley

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANDREW DMYTRIJUK
12/03/2018

KATHY M ROBIE SUH
12/06/2018