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APPLICATION NUMBER:

206910Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	New NDA
Application Number	206910
Priority or Standard	Standard
Submit Date	May 30, 2014
Received Date	May 30, 2014
PDUFA Goal Date	March 30, 2015
Division	Division of Hematology Products
Reviewer Name	Andrew Dmytrijuk M.D.
Review Completion Date	February 23, 2015
Established Name	Deferasirox Film-Coated Tablets
Trade Name	Jadenu
Therapeutic Class	Iron Chelator
Applicant	Novartis Pharmaceuticals Corp. One Health Plaza Building 337/B10-6 East Hanover, NJ 07936
Formulation	Film Coated Tablet
Dosing Regimen	14 mg per kg body weight once daily for patients with transfusional iron overload. 7 mg per kg body weight once daily for patients with NTDT syndromes
Indication	Treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. 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.
Intended Population	Patients 2 years of age and older with Iron Overload Due to Blood Transfusions Patients 10 years of age and older with non-transfusion-dependent thalassemia

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 206910 supporting document 1 letter date May 30, 2014 for Jadenu® (deferasirox, film coated tablet formulation) should be approved for the following indications which are the same indications as the currently approved product Exjade (deferasirox, tablet for oral suspension).

- Jadenu is indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. This indication is based on reduction in serum ferritin and liver iron concentration (LIC). (b) (4)
- Jadenu is indicated 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. This indication is based on (b) (4) of an LIC less than 5 mg Fe/g dw. (b) (4)

The Jadenu product label along with my labeling recommendations in section 9.3 Labeling Recommendations in this review should be forwarded to the sponsor. The bioavailability (based on area under the curve (AUC) of Jadenu was 36% greater compared to Exjade. After strength-adjustment, Jadenu, i.e., 360 mg strength film coated tablet was equivalent to Exjade, i.e., 500 mg strength tablet for oral suspension with respect to the mean AUC under fasting conditions. However, the mean Cmax was increased by 30% (90% confidence interval (CI): 1.2, 1.4). Therefore, sponsor proposes a Jadenu starting dose of 14 mg/kg orally once daily in patients with transfusional iron overload and 7 mg/kg orally once daily in patients with NTDT syndromes. The approved starting dose of Exjade is 20 mg/kg orally once daily in patients with transfusional iron overload and 10 mg/kg orally once daily in patients with NTDT syndromes.

1.2 Risk Benefit Assessment

The Cmax for Jadenu did not meet the standard bioequivalence criteria, showing an approximate 30% increase over the reference formulation. This topic was discussed with FDA at a Type C meeting on July 26, 2013 and it was agreed that a registration of the new formulation is possible despite these higher Cmax values (see Meeting Minutes by Patricia Garvey, Regulatory Project Manager in the Division of Hematology Products, final signature date August 5, 2013, in IND 58554).

The sponsor cross references the safety and efficacy of Exjade in NDA 21-882 to support the current application for Jadenu NDA 206910. Exjade was first approved by the United States Food and Drug Administration (FDA) on November 2, 2005 for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adult and pediatric patients (aged 2 years and over) at doses of up to 40 mg/kg/day. On January 23, 2013 Exjade was also approved for the treatment of chronic iron overload in patients with non-transfusion-dependent thalassemia syndromes aged 10 years and older at doses of up to 20 mg/kg/day. Clinical Reviews of Exjade for these indications were completed by Dr. George Shashaty and Dr. Donna Przepiorka (Clinical Reviewers in the Division of Hematology Products) on October 26, 2005 (NDA 21-882 submission 000) and January 9, 2013 (NDA 21-882 supplement 15), respectively. Risk/benefit assessments were completed with these reviews.

The recommendation for the approval of Jadenu is based on the safety and efficacy of the marketed Exjade (deferasirox) product and the available Jadenu supportive safety information from the pharmacokinetic (PK) and bioavailability studies F2101, F2102, F2103. No new or additional safety concerns were identified in this Clinical Review of NDA 206910 for Jadenu or in the review of the Exjade Annual Report NDA 21882 supporting document 982 letter date December 19, 2014 (covering the reporting period from November 2, 2013 to November 1, 2014) completed by Dr. Andrew Dmytrijuk final signature date March 1, 2015. Overall, the risk benefit assessment favors the approval of Jadenu for the same indications as that of Exjade. Jadenu provides a swallowable tablet option of deferasirox for patients with transfusional iron overload and NTDT syndromes.

Jadenu is a film coated tablet formulation of deferasirox, which offers patients with iron overload a potentially more palatable treatment option compared to the approved Exjade which is a dispersible tablet for oral suspension formulation. Patients who can't swallow tablets still would have the option of receiving Exjade. Because the bioavailability (based on AUC) of Jadenu was 36% greater compared to Exjade, the sponsor proposes an equivalent Jadenu starting dose of 14 mg/kg orally once daily in patients with transfusional iron overload and 7 mg/kg orally once daily in patients with NTDT syndromes compared to Exjade, i.e., 20 mg/kg orally once daily in patients with transfusional iron overload and 10 mg/kg orally once daily in patients with NTDT syndromes. The proposal appears to be reasonable. Similar to Exjade the Jadenu dose adjustment during treatment for the indicated patient populations is based on serum ferritin level and LIC which limits potential overexposure to Jadenu.

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1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No post-marketing risk evaluation and mitigation strategy (REMS) is recommended for Jadenu.

1.4 Recommendations for Postmarket Requirements and Commitments

There is no clinical data available in patients who were treated with Jadenu. Bioavailability studies and PK studies supporting the approval of Jadenu were conducted in normal healthy subjects. Post-Marketing Commitments (PMCs) and Post-Marketing Requirements (PMRs) which were issued during the approval of Exjade on November 2, 2005 and January 23, 2013 should also apply to Jadenu (deferasirox film coated tablets). However, those PMCs and PMRs that have been fulfilled for Exjade can also be considered fulfilled for Jadenu. The sponsor should complete PMCs 750-1, 750-9 and PMRs 1994-1, 1994-2, 1994-3, 1994-4, 1994-5 and 1994-6. PMC 750-10 and PMR 1994-7 are currently under FDA review. The complete list of PMRs and PMCs for Exjade in NDA 22-892 is in section 8 Post-Market Experience in this review.

2 Introduction and Regulatory Background

2.1 Product Information

Jadenu (deferasirox film coated tablet) is an orally bioavailable iron chelator. The sponsor cross-references NDA 21-882 for Exjade (deferasirox, tablet for oral suspension) to support the safety and efficacy of Jadenu. Clinical Reviews of Exjade for the indications listed below were completed by Dr. George Shashaty and Dr. Donna Przepiorka (Clinical Reviewers in the Division of Hematology Products) on October 26, 2005 (NDA 21-882 submission 000) and January 9, 2013 (NDA 21-882 supplement 15), respectively. Exjade was granted accelerated approval on November 2, 2005 for the following indication.

- Exjade is indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. This indication is based on reduction in serum ferritin and liver iron concentration (LIC). An improvement in survival or disease-related symptoms has not been established.

Exjade was granted accelerated approval on January 23, 2013 for the following indication.

- Exjade is indicated 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. This indication is based on achievement of an LIC less than 5 mg Fe/g dw. An improvement in survival or disease-related symptoms has not been established.

In NDA 206910 supporting document 1 letter date May 30, 2014 the sponsor proposes that Jadenu is indicated for the same indications as Exjade, i.e.:

- Jadenu is indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. This indication is based on reduction in serum ferritin and liver iron concentration (LIC). (b) (4)

- Jadenu is indicated 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. This indication is based on (b) (4) of an LIC less than 5 mg Fe/g dw. (b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

The reviewer's table below shows the currently available treatments and their indications.

Table 1. Currently Available Treatments for Proposed Indications

Generic Name	Deferasirox	Deferiprone	Deferoxamine
Trade Name	Exjade	Ferriprox	Desferal
NDA Number	21-882	21-825	16-267
Sponsor	Novartis Pharmaceuticals Corp.	Apopharma Inc.	Novartis Pharmaceuticals Corp.
Dosage Form	Tablet for Oral Suspension	Film Coated Tablet	Powder For Injection Solution
Original Approval Date	November 2, 2005	October 14, 2011	April 1, 1968
Indication(s)	Exjade is indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. This indication is based on reduction in serum ferritin and liver iron concentration (LIC). An improvement in survival or disease-related symptoms has not been established. Exjade is indicated 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	Ferriprox is indicated for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. Approval is based on a reduction in serum ferritin levels. There are no controlled trials demonstrating a direct treatment benefit, such as improvement in disease-related symptoms, functioning, or increased survival.	Desferal is indicated for the treatment of acute iron intoxication and of chronic iron overload due to transfusion-dependent anemias.

	300 mcg/L. This indication is based on achievement of an LIC less than 5 mg Fe/g dw. An improvement in survival or disease-related symptoms has not been established.		

Reviewer's table

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient for Jadenu is the same as that for Exjade, i.e., deferasirox. Exjade's dosage form is a tablet for oral suspension. Exjade was originally approved for marketing in the United States on November 2, 2005.

2.4 Important Safety Issues With Consideration to Related Drugs

The safety concerns for Jadenu are the same as for Exjade. The Exjade product label contains a Boxed Warning that has the following wording.

Figure 1. Exjade Boxed Warning

WARNING: RENAL FAILURE, HEPATIC FAILURE, AND GASTROINTESTINAL HEMORRHAGE

Renal Failure

- **Exjade can cause acute renal failure and death, particularly in patients with comorbidities and those who are in the advanced stages of their hematologic disorders.**
- **Measure serum creatinine and determine creatinine clearance in duplicate prior to initiation of therapy and monitor renal function at least monthly thereafter. For patients with baseline renal impairment or increased risk of acute renal failure, monitor creatinine weekly for the first month, then at least monthly. Consider dose reduction, interruption, or discontinuation based on increases in serum creatinine [see *Dosage and Administration (2.4, 2.5), Warnings and Precautions (5.1)*].**

Hepatic Failure

- **Exjade can cause hepatic injury including hepatic failure and death.**
- **Measure serum transaminases and bilirubin in all patients prior to initiating treatment, every 2 weeks during the first month, and at least monthly thereafter.**
- **Avoid use of Exjade in patients with severe (Child-Pugh C) hepatic impairment and reduce the dose in patients with moderate (Child Pugh B) hepatic impairment [see *Dosage and Administration (2.4), Warnings and Precautions (5.2)*].**

Gastrointestinal Hemorrhage

- **Exjade can cause gastrointestinal (GI) hemorrhages, which may be fatal, especially in elderly patients who have advanced hematologic malignancies and/or low platelet counts.**
- **Monitor patients and discontinue Exjade for suspected GI ulceration or hemorrhage [see *Warnings and Precautions (5.3)*].**

Exjade Label Boxed Warning (see website http://www.us.exjade.com/index.jsp?redirect=lightbox last accessed February 15, 2015)

In addition, the Exjade product label has the following Limitation of Use.

- Controlled clinical trials of Exjade with myelodysplastic syndromes (MDS) and chronic iron overload due to blood transfusions have not been performed.
- The safety and efficacy of Exjade when administered with other iron chelation therapy have not been established.

The sponsor proposes the same Boxed Warning and Limitation of Use for Jadenu as that of Exjade.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following key meetings were held with the sponsor.

- IND 58554 deferasirox –
  - February 27, 2012: Type C meeting (see Meeting Minutes by Mara Miller, Regulatory Project Manager in the Division of Hematology Products final signature date March 2, 2012). The sponsor informed FDA of their plan to develop a new formulation of deferasirox, i.e., a film coated tablet. During this meeting the sponsor informed FDA that the new formulation, i.e., film coated tablet has shown a higher Cmax value in pharmacology studies

F2102 (b) (4) (discussed in Section 4.4 Clinical Pharmacology in this review) and proposed registration of a reduced dosage strength with a matching systemic exposure profile to the currently marketed commercial formulation (Exjade). The sponsor asked if registration of the new tablet formulation could be achieved using the reduced dosage strength approach. FDA responded that the scenario described was acceptable and a final determination would be based on review of the final study reports and data.

- July 26, 2013: Type C meeting (see Meeting Minutes by Patricia Garvey, Regulatory Project Manager in the Division of Hematology Products final signature date August 5, 2013).
- March 24, 2014 Pre-sNDA meeting. The meeting was cancelled by the sponsor after the sponsor received preliminary responses to the meeting questions from the FDA (see Meeting Request Cancellation Form by Tinya Sensie, Regulatory Project Manager in the Division of Hematology Products final signature date March 24, 2014).

Reviewer comment for section 2. The sponsor proposes the same indications and labeling information for Jadenu as for Exjade with the exception that the proposed starting dose of Jadenu is 14 mg/kg orally once daily in patients with transfusional iron overload and 7 mg/kg orally once daily in patients with NTDT syndromes compared to Exjade, i.e., a starting dose of 20 mg/kg orally once daily in patients with transfusional iron overload and 10 mg/kg orally once daily in patients with NTDT syndromes. Clinical Review comments on the Clinical Pharmacology issues are in section 4.4 Clinical Pharmacology in this review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

On July 24, 2014, the Division of Hematology Products (DHP) requested inspections of the clinical and analytical sites for the following study conducted from July 2012 to October 2012 for Study CICL670F2102 titled, "A Randomized, Open-Label, Single-Center, Phase 1, Cross-Over Study to Evaluate the Pharmacokinetic Comparability of Deferasirox New Tablet Formulation with the Reference Dispersible Formulation In Healthy Subjects". The Clinical and Analytic study sites were as follows.

- Clinical site:
  PPD Phase I Clinic
  7551 Metro Center Drive, Suite 200
  Austin, TX 78744

- Analytical site:

The Division of Scientific Inquiry (DSI) consult review by Dr. Jyoti Patel final signature date October 22, 2014 states that no significant adverse observations were identified during the previous inspections at both the sites. The previous inspectional outcomes provide assurance that the sites conducted study CICL670F2102 without significant irregularities.

3.2 Compliance with Good Clinical Practices

All studies were conducted in compliance with the current revision of the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practices and local regulatory requirements. The protocols and any amendments were approved by an Institutional Review Board prior to initiation and implementation of the studies and changes. Written informed consent provided by the patient was required in order to enroll into the studies supporting NDA 206910 The informed consent, protocol violations and site-specific issues were reviewed and found to be within accepted standards.

3.3 Financial Disclosures

No investigators participating in the trials supporting NDA 206910 reported a financial interest. The sponsor states that no clinical investigators are full or part-time employees of Novartis Pharmaceuticals Corporation.

Reviewer comment for section 3: The DSI investigation did not report any major study violations. All studies were conducted in compliance with the current revision of the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practices and local regulatory requirements. No investigators in the studies supporting NDA 206910 reported an equity interest.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Dr. Debasis Ghosh (CMC Reviewer) did not report any CMC concerns in his review final signature date November 20, 2014.

4.2 Clinical Microbiology

The Product Quality Microbiology review of NDA 206910 by Dr. Bryan Riley (OPS Review) final signature date August 1, 2014 states that NDA 206910 for Jadenu does not include a Microbial Limits specification for drug product release or stability; however, the sponsor provides a suitable rationale for the exclusion of this testing. Dr. Riley states in his review that this submission is recommended for approval from the standpoint of product quality microbiology.

4.3 Preclinical Pharmacology/Toxicology

Dr. Christopher Seth (Division of Hematology Oncology Toxicology Reviewer) states in his review of NDA 206910 final signature date January 21, 2015 that the proposed nonclinical sections of the Jadenu label are similar to those for the Exjade label with the exception of a labeling format update to reflect the newly published Pregnancy Lactation and Labeling Rule in addition to having different trade names. The nonclinical sections of the Jadenu label were also updated to reflect the change in maximum recommended dose from 20 mg/kg for Exjade to 14 mg/kg for Jadenu. To maintain consistency the Jadenu label retains comparisons of dose based on body surface area. There are no nonclinical issues to preclude the approval of Jadenu for the proposed indications.

4.4 Clinical Pharmacology

Dr. Wenchi Hsu (Clinical Pharmacology Reviewer) states in her review of NDA 206910 final signature date February 3, 2015 that the bioavailability based on AUC of Jadenu was 36% greater compared to Exjade. After strength-adjustment, Jadenu, i.e., 360 mg strength film coated tablet was equivalent to Exjade, i.e., 500 mg strength tablet for oral suspension with respect to the mean AUC under fasting conditions. However, the mean Cmax was increased by 30% (90% confidence interval (CI): 1.2, 1.4). Jadenu was equivalent to Exjade with respect to the mean AUC under fasting conditions, however the mean Cmax was increased by 30%. Dr. Hsu states in her review that the Cmax values for Jadenu are within range of those observed with Exjade in healthy volunteers and patients. Furthermore, exposure-response analysis for safety was conducted by the sponsor using data from clinical trials with Exjade to evaluate the effect of a 30% increase in Cmax. Dr. Hsu states that based on the results from exposure-response analysis, the moderately higher Cmax values observed with the new FCT formulation are not expected to be clinically meaningful.

Reviewer comment for Section 4. Jadenu did not meet the standard bioequivalence criteria. A 36% greater bioavailability based on AUC for Jadenu was observed compared to Exjade. After strength-adjustment, Jadenu, i.e., 360 mg strength film coated tablet was equivalent to Exjade, i.e., 500 mg strength tablet for oral suspension with respect to the mean AUC under fasting conditions. However, the mean Cmax was increased by 30% (90% confidence interval (CI): 1.2, 1.4) showing an approximate 30%

increase over the reference formulation. This topic was discussed with FDA at a Type C meeting on July 26, 2013 and it was agreed that a registration of the new formulation could be achieved despite these higher Cmax values after review of the data. There were no other concerns identified by other review disciplines. The implication of a higher Cmax and bioavailability is that this may increase the risk for adverse reactions, such as renal and hepatic failure and gastrointestinal hemorrhage that are reported for Exjade. However, the sponsor proposes an equivalent Jadenu starting dose of 14 mg/kg orally once daily in patients with transfusional iron overload and 7 mg/kg orally once daily in patients with NTDT syndromes compared to Exjade, i.e., 20 mg/kg orally once daily in patients with transfusional iron overload and 10 mg/kg orally once daily in patients with NTDT syndromes. Dose adjustments for Jadenu and Exjade are based on responses in serum ferritin and LIC. For patients with transfusional iron overload after commencing therapy, serum ferritin should be monitored monthly and the dose of deferasirox adjusted, if necessary, every 3-6 months based on serum ferritin trends which is the same as that recommended in the Exjade product label. For patients with NTDT syndromes the sponsor proposes that serum ferritin should be monitored monthly, treatment should be interrupted when serum ferritin is less than 300 µg/L, LIC should be obtained to determine whether the LIC has fallen to less than 3 mg Fe/g dw and LIC should be monitored every 6 months which is the same as that recommended in the Exjade product label.

5 Sources of Clinical Data

5.1 Table of Studies

The sponsor's table below shows the studies included to support NDA application 206910 for Jadenu. (b) (4) This review focuses only on data concerning the film coated tablet formulation of deferasirox, i.e., Jadenu.

Table 2. Table of Studies

Protocol No. & Study Dates Investigator & Country Publication Reference	Study Design & Purpose Population Studied Evaluations	Total No.& Race (w,b,a,o) Age Range (mean) Group No. & Sex (m,f)	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status Type of Report General Results
protocol: [CICL670F2101] **countries: US** **start:** 18-Apr-2011 **end:** 10-Jul-2011 **publ.:** none	**design, goal & population:** **design:** This was a randomized, open-label, single-center, four-period, cross-over, Phase I bioavailability study with three newly developed single-dose deferasirox formulations compared to the marketed reference formulation. **goal:** The primary objective was to evaluate the bioavailability of deferasirox from the new formulations, Variant A (an oral tablet of wet granulation with low pluronic surfactant at 500 mg), Variant B (an oral tablet of wet granulation with medium pluronic surfactant at 500 mg), and Variant C (an oral tablet of wet granulation, medium pluronic surfactant, and modified-release enteric coating at	**total:** 32 (3w, 28b, 1o) **age:**23-54 (35.3) **groups:** 5 (30m, 2f) no sequence group only received iron supplementation n=11 (10m, 1f) Group 1 n= 5 (5m) Group 2 n= 6 (6m) Group 3 n= 5 (5m) Group 4 n= 5 (4m, 1f)	**treatment:** The supportive treatment was an iron supplement, ferrous sulfate 325-mg strength oral tablet, which was equivalent to 65 mg Fe++ (elemental iron). Variant A (Treatment A): Deferasirox wet granulation formulation with low pluronic surfactant, oral tablets of 500 mg dose strength. Variant B (Treatment B): Deferasirox wet granulation formulation with medium pluronic surfactant, oral tablets of 500 mg dose strength. Variant C (Treatment C): Deferasirox wet granulation formulation with medium pluronic surfactant and modified release enteric coating,	**status:** final **report:** full **report date:** 10-Nov-2011 **general results:** This study demonstrated greater bioavailability of deferasirox with all of the new variants as compared to the reference formulation. Variants A and B revealed 36% to 39% greater exposure (AUCinf) as well as 39% to 46% higher Cmax than the reference formulation. Since the difference in both AUCinf and Cmax was found to be statistically significant, it is highly unlikely that Variants A and/or B could be bioequivalent to the reference formulation. Variant C showed a modest increase of 13% to 15% in bioavailability as compared to the reference formulation. Given the 90% CI of 0.97-1.32 (for AUCinf), Variant C could potentially

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	500 mg) in comparison to the reference marketed deferasirox formulation (a dispersible tablet for oral suspension at 500 mg) [Variant D], in healthy subjects under fasted conditions. The key secondary objective was to evaluate the safety and tolerability of deferasirox from the new formulations Variant A, Variant B, and Variant C in comparison to the reference marketed deferasirox formulation (Variant D) in healthy subjects under fasted conditions.**population:** The study included a homogeneous population of healthy subjects who were treated under fasted conditions. **evaluations:** **pharmacokinetics:** Plasma deferasirox concentrations were determined on Days 1, 8, 15, and 22 at the following		oral tablets of 500 mg dose strength. Deferasirox (Treatment D): The commercial formulation of deferasirox, 500 mg dispersible tablet for oral suspension. **form(s):** 4 different tablet formulations **regimen:** Group 1 treatment sequence A/B/C/D Group 2 treatment sequence B/D/A/C Group 3 treatment sequence C/A/D/B Group 4 treatment sequence D/C/B/A **duration:** The total study duration was approximately 76 days. The screening period (Day -21 to Day -15) was followed by an 8-day iron supplement period, followed by a 6-day iron washout.	demonstrate bioequivalence to the reference formulation if the sample size is increased. Cmax and AUC for Variant C were slight more varied (CV range, 54% to 61%) as compared with that of the reference formulation (31% to 49%). As the variability was higher, Variant C does not appear to be a favorable formulation. The safety data observed during the study were within the known safety profile as described in the current labeling for Exjade.

Protocol No. & Study Dates Investigator & Country Publication Reference	Study Design & Purpose Population Studied Evaluations	Total No.& Race (w,b,a,o) Age Range (mean) Group No. & Sex (m,f)	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status Type of Report General Results
	time points: Pre-dose (0), 0.5 h, 1.0 h, 1.5 h, 2.0 h, 3.0 h, 4.0 h, 6.0 h, 8.0 h, 12.0 h, 24.0 h, 36.0 h, 48.0 h, and 72.0 h post-dose. **safety:** Safety assessments consisted of collecting all adverse events, serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of hematology, blood chemistry, and urine performed at the local laboratory and regular assessments of vital signs, physical condition, body weight, and ECG. Interpretation of the 12-lead ECG tracing was assessed by the investigator, or her designee, and documented in the eCRF.		The baseline visit (Day -1) included randomization to a treatment sequence. Dosing occurred only on the first day of each treatment period for a total of 4 treatment periods. The first three treatment periods were 7 days in duration, followed by the last treatment period of 4 days. Periods 1, 2 and 3 were separated by a 6-day washout. The End of Treatment visit occurred on Day 25. Subjects were followed up to 30 days for safety observations with the study concluding at the End of Study visit on Day 55. **dosing**: Subjects were to swallow three 500 mg tablets of investigational product (Variants A - Wet granulation, low pluronic surfactant, oral	

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			tablet, B - Wet granulation, medium pluronic surfactant, oral tablet, or C - Wet granulation, medium pluronic surfactant, modified release film-coated tablet) followed by 240 mL of water immediately afterwards. For investigational product Variant D – Commercial Dispersible tablet, the investigator (or designee) was to dissolve three tablets in 200 mL of water in a glass. With Variant D only, the glass was rinsed with an additional 40 mL of water and the subject ingested the full contents of the glass.	

Protocol No. & Study Dates Investigator & Country Publication Reference	Study Design & Purpose Population Studied Evaluations	Total No.& Race (w,b,a,o) Age Range (mean) Group No. & Sex (m,f)	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status Type of Report General Results
protocol: [CICL670F2102] **countries:** **start:** 19-Jul-2012 **end:** 27-Sep-2012 **publ.:** none	**design, goal & population:** **design** This was a randomized, open-label, single-center, two-period cross-over, single-dose Phase I study in healthy subjects to demonstrate the pharmacokinetic (PK) comparability of deferasirox as a new oral film-coated tablet (FCT) vs. the reference dispersible tablet (DT) formulation for oral suspension used commercially. **goal** The primary objective was to evaluate the PK comparability of deferasirox with a reduced dosage strength of the new oral film-coated tablet formulation (FCT) vs. the reference marketed dispersible tablet formulation (DT) in healthy subjects under fasted conditions. The secondary objectives were to evaluate the safety and tolerability of deferasirox new FCT formulation in	**total:** 44 (30w, 14b) **age:**18-55 (34.61) **groups:** 3 (33m, 11f) no sequence group only received iron supplementation n= 10 (9m, 1f) Group 1 n= 17 (12m, 5f) Group 2 n= 17 (12m, 5f)	**treatment:** The supportive treatment was an iron supplement, ferrous sulfate 325-mg strength oral tablet, which was equivalent to 65 mg Fe++ (elemental iron). Treatment A: single dose of 1080 mg deferasirox swallowable tablets Treatment B: single dose of 1500 mg deferasirox (Exjade®) commercial dispersible tablets **form(s):** film-coated tablet and dispersible tablet **regimen:** Group 1 treatment sequence A/B Group 1 treatment sequence B/A **duration:** The total duration of treatment for an	**status:**final **report:**full **report date:** 29-Apr-2013 **general results:** Bioavailability data (AUClast and AUCinf) revealed pharmacokinetic comparability between the two formulations as demonstrated by point estimates and confidence intervals (90% CI) of 1.00 (0.932-1.078) and 0.98 (0.916-1.059), respectively, when comparing FCT vs. DT. Following the single 1500-mg dose delivered as the DT (the reference), deferasirox Cmax averaged 81.54 µmol/L vs. an average Cmax of 105.83 µmol/L following the single 1080 mg dose of FCT. This yielded peak deferasirox concentrations 30% higher (geometric mean ratio, 1.30; 90% CI: 1.203-1.400) with FCT vs. the DT. These values did not meet the requirements for bioequivalence. The safety data observed during

Protocol No. & Study Dates Investigator & Country Publication Reference	Study Design & Purpose Population Studied Evaluations	Total No.& Race (w,b,a,o) Age Range (mean) Group No. & Sex (m,f)	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status Type of Report General Results
	comparison to the reference DT formulation **population** The study included a homogeneous population of healthy subjects who were treated under fasted conditions. **evaluations:** **pharmacokinetics:** Plasma deferasirox concentrations were determined on Days 1 to 4 and Days 10 to 13 at the following timepoints: 0 (pre-dose), 0.5 h, 1.0 h, 1.5 h, 2.0 h, 3.0 h, 4.0 h, 6.0 h, 8.0 h, 12.0 h, 24.0 h, 36.0 h, 48.0 h, and 72.0 h post-dose. **safety:** Safety assessments consisted of collecting all adverse events, serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of hematology, blood chemistry, and urine performed at the		individual subject was approximately 21 days (8 days of iron supplementation and 13 days including the two treatment periods). The screening period (Day -28 to Day -15) was followed by an 8-day iron supplement period (Day -14 to Day -7), which was followed by a 6-day iron washout. The baseline visit (Day -1) included randomization to a treatment sequence. Dosing occurred on the first day of each treatment period for a total of 2 periods. Periods 1 and 2 were separated by an 8-day washout. The End of Treatment (EOT) visit (Day 13) occurred 72 hours after the last dose. Subjects were followed for 30 days for safety observations with the study concluding at the	the study was consistent with the known safety profile as described in the core datasheet for Exjade.

Protocol No. & Study Dates Investigator & Country Publication Reference	Study Design & Purpose Population Studied Evaluations	Total No.& Race (w,b,a,o) Age Range (mean) Group No. & Sex (m,f)	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status Type of Report General Results
	central laboratory and regular assessments of vital signs, physical condition, body weight, and ECG. Interpretation of the 12-lead ECG tracing was assessed by the Investigator, or her designee, and documented in the eCRF.		End of Study visit (Day 43). **dosing**: Treatment A: single dose of 1080 mg deferasirox swallowable tablet formulation (360mg× 3) Treatment B: single dose of 1500 mg deferasirox (Exjade®) with commercial dispersible tablets (500mg × 3) for oral suspension	
protocol: [CICL670F2103] **countries: US** **start:** 08-Jul-2013 **end:** 05-Nov-2013 **publ.:** none	**design, goal & population**: **design:** This was a single-center, open-label, randomized, three-period, six sequence cross-over dosing study evaluating the effect of food on deferasirox pharmacokinetics in healthy subjects. A new film coated tablet formulation of deferasirox was evaluated under fasted, low-fat breakfast, and high-fat breakfast conditions. **goal:**	**total**: 37 (18w, 15b, 4o) **age**:21-53 (34.3) **groups**: 7 (15m, 22f) no sequence group only received iron supplementation n= 9 (4m, 5f) Group 1 n= 6 (1m, 5f) Group 2 n= 4 (1m, 3f) Group 3 n= 5 (2m, 3f) Group 4 n= 4 (1m, 3f) Group 5 n= 4 (2m, 2f) Group 6 n= 5 (4m, 1f)	**treatment:** Supportive therapy: Ferrous sulfate as 325-mg; (equivalent to 65 mg elemental iron); Treatment A: single dose of 1080 mg deferasirox film-coated tablet formulation under fasting conditions Treatment B: single dose of 1080 mg deferasirox film-coated tablet formulation with a low-fat breakfast Treatment C: single	**status**:final **report**:full **report date**:13-Mar-2014 **general results**: With a low-fat meal, the plasma exposure (AUClast and AUCinf) of a single oral dose of 1080 mg deferasirox FCT was comparable when compared to the fasted conditions although the Cmax decreased by 16%. Compared to the fasted condition, the estimated geometric mean ratios for AUClast, AUCinf and Cmax with low-fat breakfast were 0.89

Protocol No. & Study Dates Investigator & Country Publication Reference	Study Design & Purpose Population Studied Evaluations	Total No.& Race (w,b,a,o) Age Range (mean) Group No. & Sex (m,f)	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status Type of Report General Results
	The primary objective was to evaluate the effect of food on the PK of deferasirox new FCT formulation administered under fasted conditions and with low-fat and high-fat breakfast. The secondary objective was to evaluate the safety and tolerability of deferasirox new FCT formulation **population:** A minimum of 24 healthy male and/or female subjects were to be enrolled in order to obtain at least 18 evaluable subjects for the statistical analysis of the primary objective. **evaluations**: **pharmacokinetics:** Plasma deferasirox concentrations were determined on Days 1 through 4, 10 to 13 and 19 to 22 of Treatment Periods 1, 2 and 3 at the following time points: 0 (pre-dose) and at 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h, 36 h,		dose of 1080 mg deferasirox film-coated tablet formulation with a high-fat breakfast **form(s)**: Film coated tablet (FCT) **regimen:** Group 1 treatment sequence A/B/C Group 2 treatment sequence B/C/A Group 3 treatment sequence C/A/B Group 4 treatment sequence A/C/B Group 5 treatment sequence B/A/C Group 6 treatment sequence C/B/A **duration**: Iron supplement: 8 days, followed by 6-day washout. Treatment Periods 1 and 2 were for 9 days (an eight days wash out period between Period 1 and Period 2) while	(90% CI: 0.84, 0.94), 0.89 (90% CI: 0.84, 0.95), and 0.84 (90% CI: 0.77, 0.90), respectively. With a high-fat meal, the plasma exposure (AUCinf) and peak concentration (Cmax) of a single oral dose of 1080 mg deferasirox FCT were increased by 18% and 29%, respectively, when compared to that under fasted conditions. Compared to the fasted condition, the estimated geometric mean ratios for AUClast, AUCinf and Cmax with high-fat breakfast were 1.17 (90% CI: 1.11, 1.24) and 1.18 (90% CI: 1.11, 1.25), and 1.29 (90% CI: 1.20, 1.39), respectively. The administration of a single oral dose of 1080 mg deferasirox FCT formulation under fasted conditions or under fed conditions was well tolerated as no major safety findings were reported.

Protocol No. & Study Dates Investigator & Country Publication Reference	Study Design & Purpose Population Studied Evaluations	Total No.& Race (w,b,a,o) Age Range (mean) Group No. & Sex (m,f)	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status Type of Report General Results
	48 h, and 72 hours post-dose. **safety:** Safety assessments consisted of collecting all AEs, serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of hematology, blood chemistry and urine performed at central laboratory and regular assessments of vital signs, physical condition, body weight and ECG. Interpretation of the 12-lead ECG tracing was assessed by the Investigator or designee, and documented in the eCRF.		Treatment Period 3 was for 4 days. The End of Treatment (EOT) Visit was conducted on Day 22 i.e., 72 hours after the last dose of deferasirox. An End of Study (EOS) evaluation was conducted 30 days after the End of Treatment Visit. The total duration of the study for an individual subject was approximately 8 weeks with an additional screening time of a maximum of 14 days. **dosing**: Treatment A: The subjects will swallow three 360 mg film-coated tablets for a total of 1080 mg, with a glass of water (240 mL), in the morning after an overnight fast (last meal or snack taken at least 10 hours earlier). Treatment B: The subjects will swallow three 360 mg	

Protocol No. & Study Dates Investigator & Country Publication Reference	Study Design & Purpose Population Studied Evaluations	Total No.& Race (w,b,a,o) Age Range (mean) Group No. & Sex (m,f)	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status Type of Report General Results
			film-coated tablets for a total of 1080 mg, with a glass of water (240 mL), 30 minutes after the start of the low-fat breakfast. The entire low-fat breakfast should be consumed by the subject prior to dosing. Treatment C: The subjects will swallow three 360 mg film-coated tablets for a total of 1080 mg, with a glass of water (240 mL), 30 minutes after the start of the high-fat breakfast. The entire high-fat breakfast should be consumed by the subject prior to dosing.	

Sponsor's table NDA 206910 section 5.2 Tabular list of Clinical Studies

5.2 Review Strategy

Clinical review of the studies shown in section 5.1 Tables of Studies are in this review. This Clinical Review for Jadenu (NDA 206910) focuses on the available safety information from study F2101, F2102, F2103. Note that the sponsor cross references

the safety and efficacy of Exjade in NDA 21-882 to support the current application for Jadenu NDA 206910. Clinical Reviews of Exjade for the indications listed below were completed by Dr. George Shashaty and Dr. Donna Przepiorka (Clinical Reviewers in the Division of Hematology Products) on October 26, 2005 (NDA 21-882 submission 000) and January 9, 2013 (NDA 21-882 supplement 15), respectively.

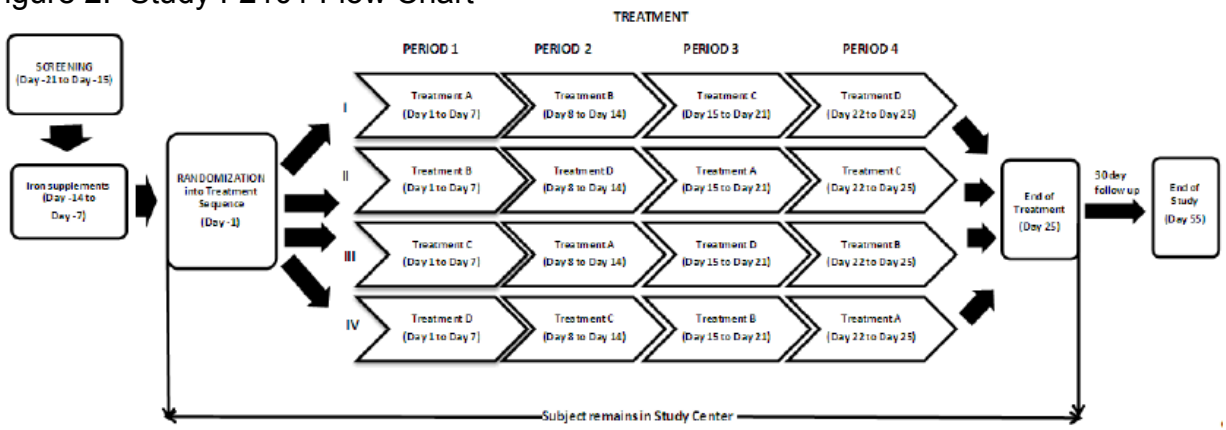
5.3 Discussion of Individual Studies

Studies supporting the Jadenu application NDA 206910 are described in section 5.1 Table of Studies in this review, i.e., studies F2101, F2102 and F2103. The following is a brief discussion of these three studies.

- F2101

  This was a randomized, open-label, single-center, four-period, cross-over, Phase 1 bioavailability study with three newly developed single-dose deferasirox formulations compared to the marketed reference formulation, i.e., Exjade (tablet for oral suspension) (n=32 normal healthy subjects). The objective of this study was to evaluate the bioavailability of deferasirox from the new formulations, i.e., Variant A (an oral tablet (b) (4) 500 mg), Variant B (an oral tablet (b) (4) 500 mg), and Variant C (an oral tablet (b) (4) modified release enteric coating at 500 mg) in comparison to Variant D (the reference marketed deferasirox formulation (tablet for oral suspension at 500 mg) in healthy adult subjects under fasted conditions. Plasma deferasirox concentrations were evaluated on Days 1, 8, 15, and 22. Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs) and clinical laboratory evaluations. The study flow chart is shown in the sponsor's figure below.

Figure 2. Study F2101 Flow Chart



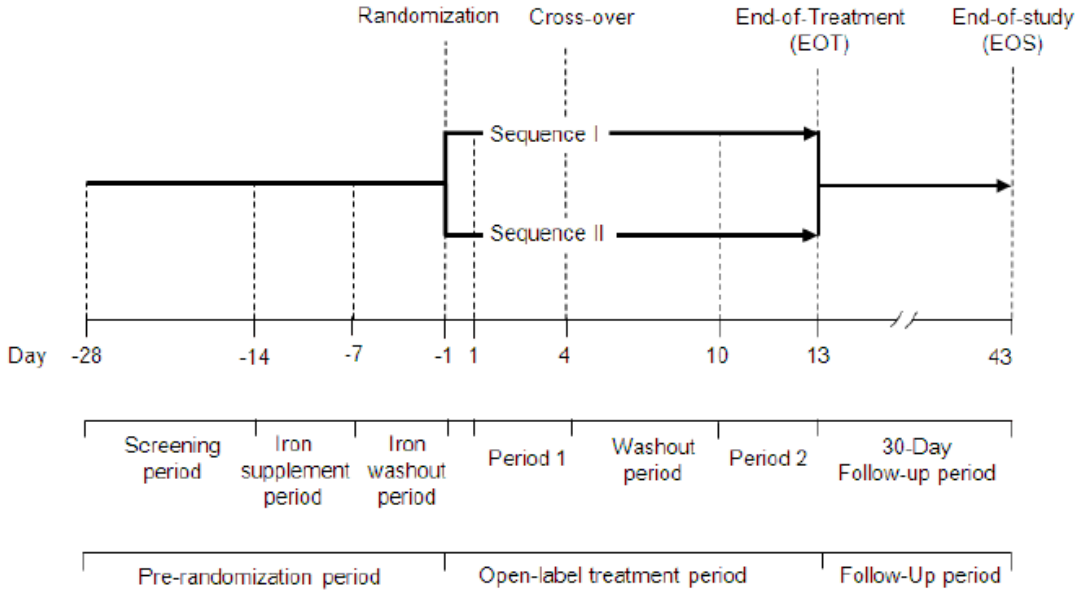
A Williams Square design was utilized for randomization of the deferasirox treatment sequences (sequence no., variant name) in the following order: (a) Sequence I [A, B, C, D]; (b) Sequence II [B, D, A, C]; (c) Sequence III [C, A, D, B]; and (d) Sequence IV [D, C, B, A]. Deferasirox dosing occurred on the first day of each of the 4 open-label treatment periods. There was a 6-day washout between treatment periods.

Sponsor's figure Study Report CICL670F2101 page 28

- F2102

This was a randomized, open-label, single-center, two-period cross-over, single dose, Phase 1 study in healthy adult subjects to demonstrate the pharmacokinetic (PK) comparability of deferasirox as a new oral film-coated tablet compared to the reference deferasirox formulation tablet for oral suspension (n=44 normal healthy subjects). The primary objective was to evaluate the PK comparability of deferasirox with a reduced dosage strength of the oral film-coated tablet formulation, i.e., 1080 mg dose compared to the reference formulation, i.e., 1500 mg dose. Plasma deferasirox concentrations were evaluated on Days 1 to 4 and Days 10 to 13. Safety assessments consisted of collecting all adverse events, serious adverse events (SAEs) and clinical laboratory evaluations. The study flow chart is shown in the sponsor's figure below.

Figure 3. Study F2102 Flow Chart



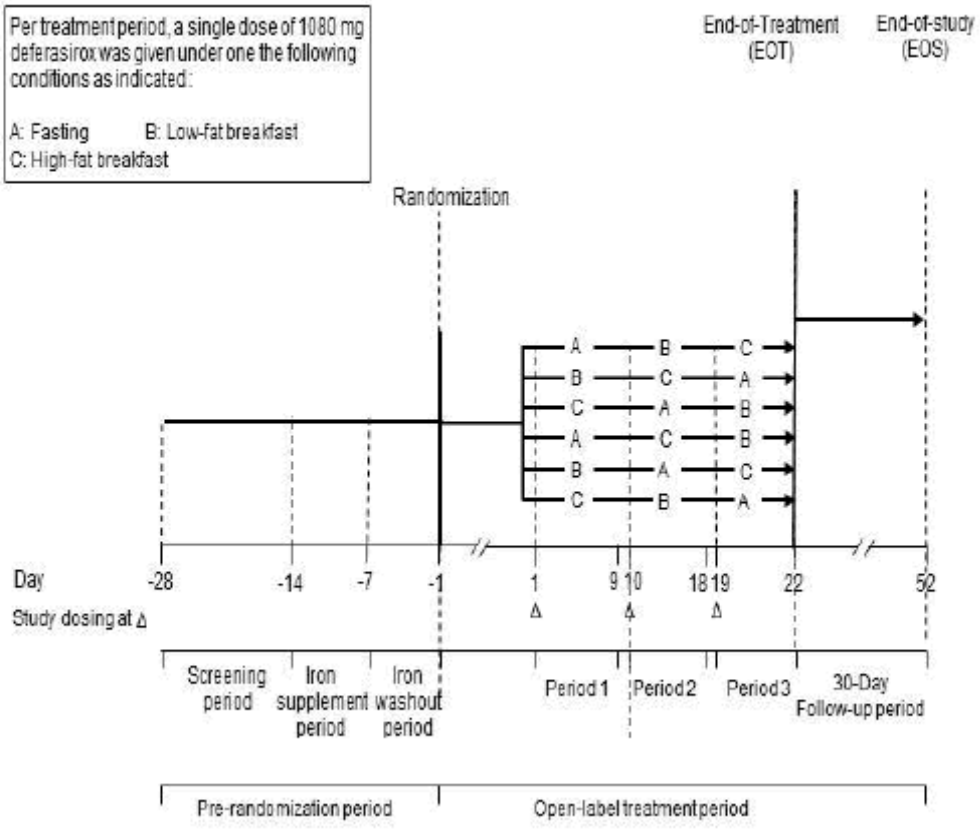
EOS = End of Study visit; EOT = End of Treatment visit
A Williams Square design was utilized for randomization of the deferasirox treatment sequences (sequence no., treatment name) in the following order: (a) Sequence I [FCT, DT]; and (b) Sequence II [DT, FCT]. Deferasirox dosing occurred once and on the first day of each open-label treatment period. There was a 6-day washout before randomization and an 8-day washout between treatment periods.
DT was the reference.

Sponsor's figure Study Report CICL670F2102 page 25

- F2103

This was a single-center, open-label, randomized, three-period, six sequence cross-over, Phase 1 dosing study evaluating the effect of food on deferasirox pharmacokinetics in healthy adult subjects (n=37 normal healthy subjects). The film coated tablet formulation of deferasirox was evaluated under fasted, low-fat breakfast, and high-fat breakfast conditions. The primary objective was to evaluate the effect of food on the PK of deferasirox film coated tablet formulation administered under fasted conditions and with low-fat and high-fat breakfast. Plasma deferasirox concentrations were evaluated on Days 1 through 4, 10 to 13 and 19 to 22 of Treatment Periods 1, 2 and 3. Safety assessments consisted of collecting all AEs, serious adverse events (SAEs). The study flow chart is shown in the sponsor's figure below.

Figure 4. Study F2103 Flow Chart



Sponsor's figure Study Report CICL670F2103 page 23.

Reviewer comment for section 5. From a clinical perspective the studies supporting the Jadenu application NDA 206910, i.e., F2101, F2102 and F2103, appear to be reasonably well designed to support a bioavailability and bioequivalence comparison of Jadenu (deferasirox film coated tablet) to the reference product Exjade (deferasirox tablet for oral suspension). The Clinical Pharmacology review by Dr. Wenchi Hsu final signature date February 3, 2015 states that The Office of Clinical Pharmacology, Division of Clinical Pharmacology V and Division of Pharmacometrics, has determined that there is sufficient clinical pharmacology information provided in this NDA to support an approval recommendation. The safety assessment considerations for these studies are acceptable. Routine physical examinations, evaluations for laboratory adverse reactions and clinical adverse reactions such as electrocardiographic (EKG) changes were performed.

6 Review of Clinical Efficacy

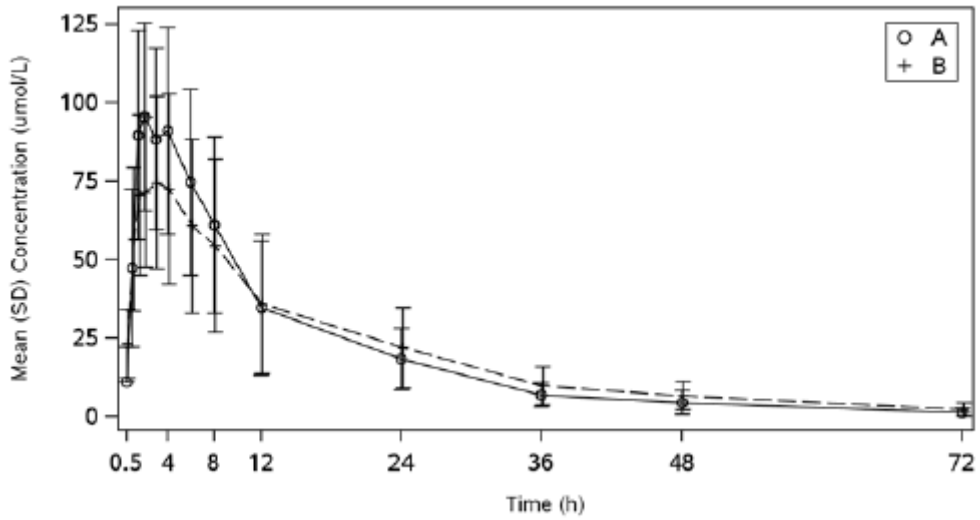
In NDA 206910 supporting document 1 letter date May 30, 2014 the sponsor proposes that Jadenu is indicated for the same indications as Exjade, i.e.,

- Jadenu is indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. This indication is based on reduction in serum ferritin and liver iron concentration (LIC). (b) (4)

- Jadenu is indicated 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. This indication is based on (b) (4) of an LIC less than 5 mg Fe/g dw. (b) (4)

The pharmacometric data for this application was reviewed by Dr. Lian Ma (Pharmacometrics Reviewer in the Division of Clinical Pharmacology V) and the review was incorporated into the Clinical Pharmacology Review by Dr. Hsu final signature date February 3, 2015. An example of the plasma deferasirox concentration-time profile observed in study F2102 is shown in the sponsor's figure below. The sponsor states that the concentration-time profiles after a single oral dose of both formulations were generally comparable except there was a higher Cmax (30% increase) in the film coated tablet group (see also Clinical Pharmacology Review of NDA 206910 by Dr. Wenchi Hsu final signature date February 3, 2015). Following a single oral dose of 1500 mg deferasirox tablet for oral suspension the mean peak plasma concentrations of deferasirox in this group was achieved at 2-3 hours post-dose. Similarly, the 1080 mg single oral dose of deferasirox film coated tablet treated group achieved mean peak deferasirox concentrations at 2-3 hours post-dose. The terminal elimination phases were comparable between the two groups, i.e., those who received deferasirox film coated tablets and those who received deferasirox tablets for oral suspension. Similar PK results were reported in the other pharmacology studies, i.e., F2101 and F2103, with the exception that the Cmax was higher by 29% in those subjects who received a high fat meal in study F2103.

Figure 4. Mean (SD) Plasma Deferasirox Concentration-Time Profile



0 = Deferiasirox film coated tablet; + = deferasirox tablet for oral suspension, SD = standard deviation.
Sponsor's figure Study Report CICL670F2102 page 51

Reviewer comment for section 6. The sponsor cross references the efficacy of Exjade in NDA 21-882 to support the current application for Jadenu NDA 206910. Clinical Reviews of Exjade for the indications listed below were completed by Dr. George Shashaty and Dr. Donna Przepiorka (Clinical Reviewers in the Division of Hematology Products) on October 26, 2005 (NDA 21-882 submission 000) and January 9, 2013 (NDA 21-882 supplement 15), respectively. Generally, the bioavailability (based on area under the curve (AUC) of Jadenu was 36% greater compared to Exjade. The PK data show that the mean Cmax was increased by 30% (90% confidence interval (CI): 1.2, 1.4) for the deferasirox film coated tablet formulation compared to the deferasirox tablet for oral suspension formulation. As stated in the reviewer comment for section 4 of this review, from a clinical perspective the implication of a higher Cmax and bioavailability is that this may increase the risk for adverse reactions which would be similar to those reported for Exjade. However, the sponsor proposes a lower equivalent Jadenu starting dose compared to Exjade. Also, proposed dose adjustments for Jadenu and Exjade during treatment are the same and are based on responses in serum ferritin and LIC. The Clinical Pharmacology review by Dr. Wenchi Hsu final signature date February 3, 2015 states that The Office of Clinical Pharmacology, Division of Clinical Pharmacology V and Division of Pharmacometrics, has determined that there is sufficient clinical pharmacology information provided in this NDA to support an approval recommendation.

7 Review of Safety

7.1.1 Methods

Studies F2101, F2102 and F2103, discussed in section 5 Sources of Clinical Data were reviewed to evaluate the safety of Jadenu in the application NDA 206910.

7.1.2 Categorization of Adverse Events

Adverse events (AEs) were characterized according to Medical Dictionary for Regulatory Activities (MedDRA) v. 17 terminology.

7.2 Adequacy of Safety Assessments

Overall 113 adult healthy male (n=78) and female (n=35) subjects ranging in age from 18-55 years were enrolled in the three pharmacology studies.

7.3 Major Safety Results

7.3.1 Deaths

No subjects died in any of the three pharmacology studies, i.e., F2101, F2102 or F2103.

7.3.2 Nonfatal Serious Adverse Events

No study drug related SAEs were reported in study F2101, F2102 or F2103. One SAE was reported in 1 subject in study F2101 who required hospitalization nephrolithiasis and was considered by investigators not to be related to study drug.

7.3.3 Dropouts and/or Discontinuations

There was one subject in each treatment group in study F2102 who withdrew consent and had administrative problems and did not complete the deferasirox treatment. One subject in study F2103 was lost to follow-up in period 3.

7.3.4 Significant Adverse Events

The Exjade product label contains a Boxed Warning that states Exjade may increase the risk for renal failure, hepatic failure and gastrointestinal hemorrhage. No AEs of these types were reported in studies F2101, F2102 or F2103.

7.4.1 Supportive Safety Results

The most common adverse events reported in studies F2102 and F2103 overall are shown in the reviewer's table below. The table shows that diarrhea and headache were the most common AEs reported in these studies. Diarrhea was slightly more often reported in subjects receiving Jadenu compared to the dispersible tablet formulation of deferasirox.

Table 3. Most Common Adverse Events (AEs) in Studies F2102 and F2103

AE (>3 NHV)	Deferasirox Film Coated Tablet (n=57) n, %	Deferasirox Tablet for Oral Suspension (n-32) n,%
Diarrhea	12 (21)	3 (9)
Headache	3 (5)	2 (6)

Reviewer table derived from sponsor's table 14.3.1-1.1 Study Report CICL670F2102 page 146 and table 14.3.1-1.1 Study Report CICL670F2103 page 156

7.4.2 Laboratory Findings

Clinical laboratories that were evaluated with each period included hematologic, hepatic and renal function tests. No significant laboratory changes were reported for subjects enrolled in studies F2101, F2102 or F2103.

7.4.3 Vital Signs and Electrocardiograms (ECGs)

No significant changes in vital signs or ECGs were reported during any treatment period in studies F2101, F2102 or F2103.

7.4.4 Immunogenicity

No immunogenicity concerns are expected with the small molecule deferasirox. No immunogenicity assays were performed for Jadenu.

7.5 Additional Safety Evaluations

No additional safety evaluations were reported by the sponsor for Jadenu.

(b) (4)

(b) (4)

Reviewer comment for Section 7. Review of safety in the studies supporting the Jadenu application NDA 206910, i.e., studies F2101, F2102 and F2103, does not raise new or additional safety concerns for Jadenu compared to the marketed Exjade product. These studies were conducted in normal healthy male and female subjects. The safety labeling described in the Exjade product label is the same the safety labeling for the proposed Jadenu product label. (b) (4) *. However, it should be noted that the existing Postmarketing Requirements (PMRs) and Postmarketing commitments (PMCs) for pediatric studies of deferasirox under NDA 21882 (Exjade) should be completed and studies may be modified to allow use of the film coated tablet (Jadenu) formulation.*

8 Postmarket Experience

There are no clinical data in patients with treated with Jadenu. Clinical review of the Annual Report for Exjade NDA 21882 supporting document 982 letter date December 19, 2014 (covering the reporting period from November 2, 2013 to November 1, 2014) was completed by Dr. Andrew Dmytrijuk final signature date March 1, 2015. In his review Dr. Dmytrijuk states that a total (b) (4) doses of Exjade were distributed domestically and that no new safety issues were identified during the review of this annual report.

A number of PMCs were issued during the approval of Exjade for the indications treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older and 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 November 2, 2005 and January 23, 2013 respectively. Both indications remain under Accelerated Approval status. The status of the PMCs and

PMRs shown below was discussed by the sponsor in the Annual Report for Exjade NDA 21882 supporting document 982 letter date December 19, 2014 (covering the reporting period from November 2, 2013 to November 1, 2014). The following list summarizes the PMCs for Exjade in the November 2, 2005 Accelerated Approval Letter. The reviewer comments below summarize the current status of these PMCs.

1. Establish a registry for children aged 2 to < 6 years to enroll approximately 200 patients and follow them for 5 years. Data collection will be at least monthly for renal function and blood pressure and yearly for growth and development. Submit your monitoring scheme for our review and comment.

   Protocol Submission: by June 30, 2006
   Study Start: by December 31, 2006
   Final Report Submission: by June 30, 2012

Reviewer comment: This is currently termed PMR 750-1. Status delayed. The study is delayed as a result of issues encountered during study start-up and initial recruitment difficulties. Enrollment to the study is completed; this includes over 200 patients on study for more than 6 months. As discussed with the Agency during a Type C Meeting on July 17, 2008, Novartis will provide an interim study report on 100 patients which will be submitted to the Agency by August 2014. The final study report on 200 patients will be submitted to the Agency by February 2016.

2. Complete the extension portion of Studies 0105E2, 0106E1, 0107E1, 0108E1, and 0109E1 for a total of 4 years after the core trial (5 years total in patients initially treated with ICL670, 4 years for patients initially treated with DFO).

   Amendment Submission: by January 31, 2006
   Study Start: N/A (ongoing)
   Final Report Submission: by June 30, 2009

Reviewer comment: This is currently termed PMR 750-2. Status fulfilled (see FDA letter dated November 22, 2010).

3. Conduct a single arm study in patients with congenital or acquired anemias and chronic iron overload to obtain additional data in patients with LIC < 7 treated with Exjade® doses of 20 or 30 mg/kg per day.

   Protocol Submission: by June 30, 2006
   Study Start: by December 31, 2006
   Final Report Submission: by March 31, 2010

Reviewer comment: This is currently termed PMR 750-3. Status fulfilled (see FDA letter dated July 1, 2010).

4. Provide the full study report, including safety and efficacy datasets, for Study 0109, a study in patients with sickle cell disease.

   Final Report Submission: by January 31, 2006

Reviewer comment: This is currently termed PMR 750-4. Status fulfilled (see FDA letter dated March 6, 2007).

5. Provide an adequate proposal for assessing iron concentration and cardiac function in patients treated with Exjade®.

   Protocol Submission: by January 31, 2006
   Study Start: by April 30, 2006
   Final Study Report: by June 30, 2008

Reviewer comment: This is currently termed PMR 750-5. Status fulfilled (see FDA letter dated January 24, 2014).

In addition, the November 2, 2005 Accelerated Approval Letter for Exjade listed the following PMCs that were not a condition of the accelerated approval.

6. Complete a study to collect safety and efficacy data for Exjade® in patients with elevated baseline serum creatinine (≥ 2X ULN) in patients with low or intermediate risk MDS (e.g., Study US03, amended to include patients with baseline serum creatinine values up to 2X ULN). Duration of followup on Exjade® should be at least 3 years.

   Amendment Submission: by January 31, 2006
   Study Start: by N/A (ongoing)
   Final Report Submission: by December 31, 2009

Reviewer comment: This is currently termed PMR 750-6. Status fulfilled (see FDA letter dated August 13, 2012).

7. Conduct a single dose pharmacokinetics study of Exjade® in subjects with hepatic impairment.

   Protocol Submission: by March 31, 2006
   Study Start: by June 30, 2006
   Final Report Submission: by June 30, 2007.

Reviewer comment: This is currently termed PMR 750-7. Status fulfilled (see FDA letter dated August 11, 2011).

8. Conduct a drug-drug interaction study with midazolam to investigate the potential of Exjade® to inhibit CYP4503A4.

   Protocol Submission: by March 31, 2006
   Study Start: by June 30, 2006
   Final Report Submission: by June 30, 2007

Reviewer comment: This is currently termed PMR 750-8. Status fulfilled (see FDA letter dated June 25, 2008).

9. Complete study of long-term follow-up (3 years) in 150 patients with myelodysplastic syndromes (MDS) receiving Exjade® to evaluate safety (including cardiac, hepatic, endocrine and renal) and hematologic and clinical benefit of Exjade® in these patients.

   Amendment Submission: by January 31, 2006
   Study Start: N/A (ongoing)
   Final Report Submission: by December 31, 2009

Reviewer comment: This is currently termed PMR 750-9. Status delayed. The study supporting this PMC is Study CICL670A2302. This study is a prospective, randomized, double-blind, placebo-controlled, multicenter phase 3 study of deferasirox in patients with low/INT-1 myelodysplastic syndromes and transfusional iron overload. The sponsor states that after discussion with the Agency regarding a primary composite endpoint, the full protocol was submitted July 15, 2009 (Serial # 518). The sponsor states that the Agency has been updated regularly as to the difficulties in enrolling this trial. Protocol amendments were submitted in July 2010 and February 2011 to modify the entry criteria in order to be able to recruit more patients for the study. Assessment of this PMC will be decided after submission of the study report submitted to fulfill PMR 1994-4 discussed below.

10. Conduct an ophthalmologic study in patients receiving Exjade®. Examinations should include distance visual acuity, applanation tonometry, lens photography, and wide angle fundus photography of retina and optic nerve and should be done at baseline (prior to Exjade® initiation) and at six month intervals. At least 60 patients should complete 2 years of follow-up.

    Protocol Submission: by June 30, 2006
    Study Start: by December 31, 2006
    Final Report Submission: by March 31, 2010

Reviewer comment: This is currently termed PMR 750-10. Status - under FDA review. The clinical study report was submitted to the NDA 21-882 on September 28, 2012. Responses to FDA comments were subsequently submitted September 5, 2014.

11. Adequately address (b) (4) in the drug substance. To qualify the presence of this impurity of (b) (4) conduct a 4-week repeated dose oral toxicity study with (b) (4) in rats and de(b) (4)te that the no effect dose is at least (b) (4) i.e., ≥10 fold (b) (4) concentration than the proposed qualification level (b) (4) Th(b) (4) ould employ (b) (4). (Refer to the ICH Q3A document entitled, "(b) (4) on Impurities in New Drug (b) (4) February 2003).

    Protocol Submission: by January 31, 2006
    Study Start: by May 31, 2006
    Final Study Submission: by December 31, 2006

Reviewer comment: This is currently termed PMR 750-11. Status fulfilled (see FDA letter dated May 30, 2007).

As part of the Accelerated Approval of Exjade on January 23, 2013 the following PMRs were issued.

PMR 1994-1 Conduct a trial to assess the long-term efficacy of Exjade® (deferasirox) in patients with NTDT and high LIC. The trial should assess response rates in the subset of patients with baseline LIC values >15 mg Fe/g dw (proportion of patients achieving an LIC <5 mg Fe/g dw and time to achieving an LIC <5 mg Fe/g dw). Follow-up of all subjects for up to 5 years is necessary.

Final Protocol Submission:	09/2013
Trial Completion:	05/2019
Final Report Submission:	11/2019

Reviewer comment: Status – the study is ongoing. The sponsor states that the planned enrollment was for 117 patients and current enrollment status is 134 patients. The sponsor estimates completion of the study in November 2019.

PMR 1994-2 Assess the long-term efficacy (and safety) of Exjade® (deferasirox) treatment to a target LIC of 3 mg Fe/g dw followed by one or more treatment holidays until the LIC is ≥5 mg Fe/g dw in patients with NTDT. Follow-up of all subjects for up to 5 years is necessary.

Final Protocol Submission:	09/2013
Trial Completion:	05/2019
Final Report Submission:	11/2019

Reviewer comment: Status - the study is ongoing. The sponsor states that the planned enrollment was for 117 patients and current enrollment status is 134 patients. The sponsor estimates completion of the study in November 2019.

PMR 1994-3 Conduct a prospective, randomized trial in at least 210 patients with low to intermediate risk myelodysplastic syndromes (MDS) receiving Exjade® (deferasirox) for transfusional iron overload (approximately 140) or placebo (approximately 70) to determine the efficacy and safety of Exjade® (deferasirox) in this population. The trial will continue for 3 years from the date the last patient is enrolled.

Final Protocol Submission:	07/2013
Trial Completion:	03/2018
Final Report Submission:	09/2018

Reviewer comment: Status- the study is ongoing. The sponsor states that the planned enrollment was for 210 patients and current enrollment status is 209 patients. The sponsor estimates completion of the study in September 2018.

PMR 1994-4 Establish a registry of children (aged 10 to <18 years old at enrollment) with NTDT and treated with Exjade® (deferasirox) for documented iron overload. Study 2422 will follow at least 40 children for up to 5 years to assess and analyze the long-term safety of treatment with Exjade® (deferasirox), including an assessment of growth, compared to children on a regular transfusion program receiving Exjade® (deferasirox) (based on historical data). Provide annual interim reports on enrollment and outcomes.

The timetable you submitted on January 22, 2013 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	10/2013
Interim Report Submission:	12/2014
Interim Report Submission:	12/2015
Interim Report Submission:	12/2016
Interim Report Submission:	12/2017
Interim Report Submission:	12/2018
Interim Report Submission:	12/2019
Interim Report Submission:	12/2020
Study Completion:	06/2021
Final Report Submission:	12/2021

Reviewer comment: Status – the study is ongoing. The sponsor states that the planned enrollment was for 40 patients and current enrollment status is 2 patients. The sponsor estimates completion of the study in December 2021.

PMR 1994-5 Conduct an enhanced pharmacovigilance study (including proactive surveillance and follow-up of spontaneous reports) to characterize the frequency and severity of adverse Events of Special Interest (ESIs), defined as all deaths and severe or serious events of kidney or liver toxicity, in adults receiving Exjade® (deferasirox) for documented iron overload related to multiple transfusions for myelodysplastic syndrome with anemia requiring transfusions. The specifics regarding targeted safety data collection and analysis, case ascertainment, and processes for meaningful surveillance will be detailed in a protocol to be submitted for FDA review and concurrence prior to study initiation. This study does not replace monitoring and reporting as required by regulations.

The timetable you submitted on January 22, 2013 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	10/2013
Interim Report Submission:	07/2014
Interim Report Submission:	01/2015
Interim Report Submission:	07/2015
Interim Report Submission:	01/2016
Interim Report Submission:	01/2017
Interim Report Submission:	01/2018
Study Completion:	01/2019
Final Report Submission:	07/2019

Reviewer comment: Status – the study is ongoing. The study is a pharmacovigilance study with no planned number of enrollments. The sponsor estimates completion in July 2019.

PMR 1994-6 Assess the long-term safety of Exjade® (deferasirox) in patients with NTDT by conducting a trial of Exjade® (deferasirox) for the treatment of iron overload (LIC ≥5 mg Fe/g dw) in non-transfusion dependent thalassemia (NTDT) in patients aged 10 years and greater with up to 5 years total follow-up.

The timetable you submitted on January 22, 2013 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2013
Trial Completion:	05/2019
Final Report Submission:	11/2019

Reviewer comment: Status – the study is ongoing. The sponsor states that the planned enrollment was for 117 patients and current enrollment status is 134 patients. The sponsor estimates completion of the study in November 2019.

PMC 1994-7 Characterize the relationship between LIC and serum ferritin in patients with NTDT at the following times: when a decision on whether to initiate treatment with Exjade® (deferasirox) is being made, and during treatment at times when dose adjustment(s) may be made or when a decision on treatment discontinuation may be made. Perform an analysis of paired LIC and serum ferritin measurements obtained in studies 2209 and 2209E before, during or after treatment with Exjade to determine the positive and negative predictive values of specific thresholds of serum ferritin for LIC values of LIC >5, LIC >7, LIC >15 and LIC <3 mg Fe/g dw.

The timetable you submitted on January 22, 2013 states that you will conduct this study according to the following schedule:

Final Analysis Plan Submission:	07/2013
Analysis Completion:	10/2013
Final Report Submission:	12/2013

Reviewer comment: Status – under FDA review. The sponsor states that the Final Study Report was submitted December 26, 2013. FDA comments were received by the sponsor on March 19, 2014 and July 24, 2014. The sponsor responded to the FDA comments on September 4, 2014. FDA review is ongoing.

Reviewer comment for Section 8: There is no clinical data available in patients who were treated with Jadenu. Clinical review of the Annual Report for Exjade NDA 21882 supporting document 982 letter date December 19, 2014 (covering the reporting period from November 2, 2013 to November 1, 2014) completed by Dr. Andrew Dmytrijuk final signature date March 1, 2015 concludes that no new safety issues were identified during the review of this annual report. PMCs and PMRs which were issued during the approval of Exjade on November 2, 2005 and January 23, 2013 should also apply to Jadenu (deferasirox film coated tablets). However, those PMCs and PMRs that have been fulfilled for Exjade can also be considered fulfilled for Jadenu. The sponsor

should complete PMCs 750-1, 750-9 and PMRs 1994-1, 1994-2, 1994-3, 1994-4, 1994-5 and 1994-6. Use of the film coated tablet (Jadenu) formulation should be allowed in the Exjade PMR and PMC studies. PMC 750-10 and PMR 1994-7 are currently under FDA review.

9 Appendices

9.1 Literature Review/References

In order to determine if there is an increased risk of adverse reactions such as overchelation of body iron or other adverse reactions due to the increased bioavailability of Jadenu compared to Exjade a literature review for published reports of Exjade drug overdose was done. The review revealed no new reports of overdose other than those already described in the Exjade product label. The Exjade product label states that cases of overdose (2 to 3 times the prescribed dose for several weeks) have been reported. In 1 case, this resulted in hepatitis which resolved without long-term consequences after a dose interruption. Single doses of deferasirox up to 80 mg per kg per day with the tablet for oral suspension formulation in iron overloaded beta thalassemic patients have been tolerated with nausea and diarrhea noted. In healthy volunteers, single doses of up to 40 mg per kg per day with the tablet for oral suspension formulation were tolerated. There is no specific antidote for Exjade. In case of overdose, induce vomiting and employ gastric lavage. The Exjade product label states that for patients with transfusional iron overload, measure serum ferritin monthly to assess for possible overchelation of iron. If the serum ferritin falls below 500 µg/L, consider interrupting therapy with Exjade, since overchelation may increase Exjade toxicity. For patients with NTDT, measure LIC by liver biopsy or by using an FDA-cleared or approved method for monitoring patients receiving deferasirox therapy every 6 months on treatment. Interrupt Exjade administration when the LIC is less than 3 mg Fe/g dw. Measure serum ferritin monthly, and if the serum ferritin falls below 300 µg/L, interrupt Exjade and obtain a confirmatory LIC. The Jadenu product label contains the same description of cases where overdose of Exjade occurred.

Reviewer comment: The Exjade and proposed Jadenu product labels appear to adequately describe the risk of overdose and overchelation with deferasirox.

9.2 Advisory Committee Meeting

No Advisory Committee Meeting is planned.

9.3 Labeling Recommendations

The Jadenu label attached below incorporates the labeling recommendations from FDA review divisions and my proposed wording additions in underline and highlighted format and my proposed wording deletions in strikethrough and highlighted format. Key clinical labeling recommendations for the Jadenu product label are as follows.

27 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANDREW DMYTRIJUK
03/17/2015

KATHY M ROBIE SUH
03/17/2015