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APPLICATION NUMBER:

207968Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	New NDA
Application Number	207968
Priority or Standard	Standard
Submit Date	July 21, 2016
Received Date	July 21, 2016
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Division	Division of Hematology Products
Reviewer Name	Andrew Dmytrijuk M.D.
Review Completion Date	April 26, 2017
Established Name	Deferasirox
Trade Name	Jadenu® Sprinkle
Therapeutic Class	Iron Chelator
Applicant	Novartis Pharmaceuticals Corp. One Health Plaza Building 337/B10-6 East Hanover, NJ 07936
Formulation	Granules
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 207968 supporting document 1 letter date July 21, 2016 for Jadenu® Sprinkle (deferasirox granules) should be approved for the following indications which are the same indications as the currently approved product Exjade® (deferasirox, tablets for oral suspension, NDA 21882 (approved for marketing July 7, 2005)) and Jadenu® (deferasirox, film coated tablets, NDA 206910 (approved for marketing March 30, 2015)).

- Jadenu Sprinkle 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) (b) (4)
- Jadenu Sprinkle 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. (b) (4) (b) (4)

The bioavailability (based on area under the curve (AUC) of Jadenu Sprinkle (deferasirox granules) was 52% greater compared to Exjade. The mean Cmax was increased by 34% (90% confidence interval (CI): 1.3, 1.4). After strength-adjustment 1080mg of Jadenu Sprinkle (deferasirox granules) was equivalent to 1500 mg of Exjade (deferasirox tablets for oral suspension) with respect to the mean AUC under fasting conditions. Therefore, the sponsor proposes a Jadenu Sprinkle 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 (see Clinical Pharmacology Review by Dr. Sriram Subramaniam for NDA 207968 final signature date April 13, 2017). Notably, in bioavailability studies submitted to support the application of Jadenu (deferasirox film coated tablets, NDA 206910) that compared the AUC and Cmax of Jadenu to the Cmax was 30% (90% CI: 1.2, 1.4) higher for Jadenu compared to Exjade. However, 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. Therefore, the 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 (see Clinical Pharmacology Review by Dr. Vicky Hsu for NDA 206910 final signature date February 3, 2015). The difference of 4%

in Cmax in Jadenu Sprinkle compared to Jadenu is not clinically significant. The Jadenu Sprinkle product label along with my labeling recommendations in section 9.3 Labeling Recommendations in this review should be forwarded to the sponsor.

1.2 Risk Benefit Assessment

The bioavailability (AUC) of Jadenu Sprinkle (deferasirox granules) was 52% greater than with Exjade (deferasirox tablets for oral suspension). The Cmax for Jadenu Sprinkle did not meet the standard bioequivalence criteria, showing an approximate 34% increase over the Exjade reference formulation of deferasirox. This topic was previously discussed with FDA for the Jadenu marketing application at a Type C meeting on July 26, 2013 and it was agreed that a registration of the Jadenu (deferasirox film coated tablet formulation) was possible despite the higher Cmax value (see Meeting Minutes by Patricia Garvey, Regulatory Project Manager in the Division of Hematology Products, final signature date August 5, 2013, in IND 58554). Similarly, registration of Jadenu Sprinkle should also be possible despite the higher Cmax value compared to that of Exjade.

The sponsor cross references the safety and efficacy of Exjade in NDA 21882 to support the current application for Jadenu Sprinkle NDA 207968. 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 21882 supplement 15), respectively. Risk/benefit assessments were completed with these reviews.

The recommendation for the approval of Jadenu Sprinkle is based on the safety and efficacy of the marketed Exjade (deferasirox) product and the available Jadenu Sprinkle supportive safety information from the pharmacokinetic (PK) and bioavailability studies F2104, F2105, F2106 and F1102. No new or additional safety concerns were identified in this Clinical Review of NDA 207968 for Jadenu Sprinkle. Overall, the risk benefit assessment favors the approval of Jadenu Sprinkle for the same indications as those of Exjade, i.e., for patients with transfusional iron overload and NTDT syndromes.

Jadenu Sprinkle is a granule 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. It is intended that Jadenu Sprinkle be sprinkled onto food. Patients who can't swallow tablets would also have the option of receiving Jadenu Sprinkle or Exjade instead of Jadenu. The sponsor

proposes an equivalent Jadenu Sprinkle 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. The proposed dosing of Jadenu Sprinkle is the same as that of Jadenu. The starting dose of Jadenu Sprinkle is equivalent to the Exjade recommended starting dose, 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 Jadenu the Jadenu Sprinkle dose adjustment during treatment for the indicated patient populations is based on serum ferritin level and LIC which limits potential overexposure to Jadenu. Similar dosing adjustments are also recommended in the Exjade product label (approved August 12, 2016 under NDA 21882).

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

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

1.4 Recommendations for Postmarket Requirements and Commitments

There is no clinical data available in patients who were treated with Jadenu Sprinkle (deferasirox granules). Bioavailability studies and pharmacokinetic (PK) studies supporting the approval of Jadenu Sprinkle were conducted in normal healthy subjects. Post-Marketing Requirements (PMRs) which were issued during the approval of Jadenu on March 30, 2015 should also apply to Jadenu Sprinkle. However, those PMRs that have been fulfilled for Jadenu can also be considered fulfilled for Jadenu Sprinkle. The sponsor should complete PMRs 2888-1, 2888-2, 2888-3 and 2888-4. The complete list of PMRs for Jadenu in NDA 206910 is in section 8 Post-Market Experience in this review. Any or all of the deferasirox formulations, i.e., Exjade, Jadenu or Jadenu Sprinkle, may be used to complete the outstanding PMRs.

2 Introduction and Regulatory Background

2.1 Product Information

Jadenu Sprinkle (deferasirox granules) is an orally bioavailable iron chelator. The sponsor cross-references NDA 21882 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 submitted a marketing application for Jadenu (deferasirox film coated tablet) that has the same indications as Exjade listed above. The sponsor proposes these same indications for Jadenu Sprinkle as those for Jadenu and Exjade, i.e.:

- Jadenu Sprinkle 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) (b) (4).

- Jadenu Sprinkle 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. (b) (4) (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	Deferasirox	Deferiprone	Deferiprone	Deferoxamine
Trade Name	Exjade	Jadenu	Ferriprox	Ferriprox	Desferal
NDA Number	21882	206910	21825	208030	16267
Sponsor	Novartis Pharmaceuticals Corp.	Novartis Pharmaceuticals Corp.	Apopharma Inc.	Apopharma Inc.	Novartis Pharmaceuticals Corp.
Dosage Form	Tablet for Oral Suspension	Film Coated Tablet	Film Coated Tablet	Oral Solution	Powder For Injection Solution
Original Approval Date	November 2, 2005	March 30, 2015	October 14, 2011	September 9, 2015	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	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) (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	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.	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.

	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.	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. (b) (4) (b) (4)			

Reviewer's table

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient for Jadenu Sprinkle is the same as that for Exjade and Jadenu, i.e., deferasirox. Exjade's dosage form is a tablet for oral suspension. Jadenu's dosage form is a film coated tablet. Exjade was originally approved for marketing in the United States on November 2, 2005. Jadenu was originally approved for marketing in the United States on March 30, 2015

2.4 Important Safety Issues with Consideration to Related Drugs

The safety concerns for Jadenu Sprinkle are the same as for Exjade and Jadenu. The Exjade and Jadenu product labels contain a Boxed Warning that has the following wording (Exjade Boxed Warning shown below for reference).

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 Exjade product label approved August 12, 2016)

In addition, the Exjade and Jadenu product labels have the following Limitation of Use (Exjade Limitation of Use shown below for reference).

- Controlled clinical trials of Exjade in patients with myelodysplastic syndromes (MDS) and chronic iron overload due to blood transfusion 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 Sprinkle as that of Exjade and Jadenu.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following key meeting with the sponsor was held under IND 58554 to discuss the registration pathway for the granule formulation of deferasirox.

- Type C Written Responses Only (WRO) meeting – responses sent to sponsor on July 10, 2014.

Reviewer comment for section 2. The sponsor proposes the same indications and labeling information for Jadenu Sprinkle as for Exjade and Jadenu with the exception that the proposed starting dose of Jadenu Sprinkle 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. The dosing recommendations for Jadenu Sprinkle are the same as Jadenu. 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

The Office of Study Integrity and Surveillance (OSIS) conducted a surveillance inspection of the analytical study site listed below from February 6, 2017 to February 10, 2017. The review memorandum completed by Dr. Xikui Chen in the OSIS (final signature date February 17, 2017) states that no significant deficiencies were observed at the analytical study site and that data submitted to NDA 207968 is reliable.

(b) (4)

The Office of Study Integrity and Surveillance (OSIS) conducted a surveillance inspection of the clinical study site listed below from Study ICL670F1102 from January 23, 2017 to January 27, 2017. The review memorandum from completed by Dr. Yiyue Zhang in the OSIS (final signature date April 14, 2017) states that no significant deficiencies were observed at the clinical study site and that data submitted to NDA 207968 is reliable.

(b) (4)

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 subjects was required in order to enroll into the studies supporting NDA 207968. 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 207968 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 OSIS investigation did not report any major study violations for the analytical study site. 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 207968 reported an equity interest.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry, Manufacturing and Controls (CMC) review is ongoing.

4.2 Clinical Microbiology

The Clinical Microbiology review is ongoing.

4.3 Preclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review is ongoing. In the Pharmacology/Toxicology Review completed by Dr. Ramdevi Gudi (Pharmacology/Toxicology Filing Reviewer in the Division of Hematology Products (DHP), final signature date September 9, 2016) no filing issues were identified.

4.4 Clinical Pharmacology

Dr. Sriram Subramaniam (Clinical Pharmacology Reviewer) states in his review of NDA 207968 final signature date April 13, 2017 that the mean AUC following a single 1080mg dose of Jadenu Sprinkle was similar to that of a 1500mg dose of Exjade under

fasting condition. However, the mean Cmax following a dose of Jadenu Sprinkle was 34% higher as compared to Exjade. Dr. Subramaniam states that the difference is not clinically meaningful based on E-R analysis for safety. Similarly, the mean Cmax was higher following the same dose of Jadenu compared to Exjade and it was concluded that the differences in exposure were not clinically meaningful. The mean AUC and Cmax of Jadenu Sprinkle with a soft meal, e.g., yogurt and apple sauce or low-fat meal (~450 calories with fat content ~30% of total calories), were similar to those under fasting conditions. Also, the increase in mean AUC with a high-fat meal (~1000 calories with fat content > 50% of total calories) was within 1.2-fold with no change in mean Cmax compared to that under fasting conditions.

Reviewer comment for Section 4. Jadenu Sprinkle did not meet the standard bioequivalence criteria when compared to Exjade. A 34% greater Cmax for Jadenu Sprinkle was observed than for Exjade. After strength-adjustment, the mean AUC following a single 1080mg dose of Jadenu Sprinkle was similar to that of a 1500mg dose of Exjade under fasting condition (see Clinical Pharmacology Review by Dr. Sriram Subramaniam, final signature date April 13, 2017). This topic was previously discussed with FDA during the review of the marketing application for Jadenu 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 (see Clinical Pharmacology Review by Dr. Vicky Hsu for NDA 206910 final signature date February 3, 2015). The implication of a higher Cmax for Jadenu Sprinkle 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 Sprinkle, 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 and Jadenu product labels. 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 300µg/L, LIC should be obtained to determine whether the LIC has fallen to less than 3mg Fe/g dw and LIC should be monitored every 6 months which is the same as recommended in the Exjade and Jadenu product label. CMC, Clinical Microbiology and Pharmacology/Toxicology reviews are ongoing.

5 Sources of Clinical Data

5.1 Table of Studies

The sponsor's table below shows the studies included to support NDA application 207968 for Jadenu. This review focuses only on data concerning the granule formulation of deferasirox, i.e., Jadenu Sprinkle.

Table 2. Table of Studies

Protocol No., Study Dates, Countries & Publication References	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: [CICL670F2104] **countries:** US **start:** 12-Jul-2012 **end:** 30-Oct-2012 **publ.:** None	**design, goal & population:** **design**: This was a randomized, open-label, single-center, four-period, four-sequence cross-over, single-dose Phase I bioavailability (BA) study comparing the new deferasirox granule formulation to the reference deferasirox formulation. **goal:** **primary objective**:To evaluate the BA of a deferasirox granule formulation at doses of 400 mg, 800 mg, and 1200 mg, in comparison to the reference deferasirox (Exjade) formulation (1500 mg dose), in healthy subjects under fasted conditions.	**total**: 39 (24 w,15b) **age**: 21-51 (31.7) **groups**: 4 (34 m 5f) Group 1 (6m, 1f) Group 2 (5m) Group 3 (6m) Group 4 (4m, 2f)	Supportive therapy: Ferrous sulfate as 325-mg; (equivalent to 65 mg elemental iron); Treatment A: single dose of 1500 mg deferasirox (Exjade®) commercial dispersible tablets (DTs) Treatment B: single dose of 400 mg deferasirox granules Treatment C: single dose of 800 mg deferasirox granules Treatment D: single dose of 1200 mg deferasirox granules **forms** DT and granules. **regimen:**	**status**:Final **report**:Full **report date**: 21-Oct-2013 **general results**: This study showed comparable BA between single doses of the DT reference (1500 mg dose) and the strength-adjusted granule formulation (1200 mg dose) for AUClast and AUCinf: the geometric mean ratios for AUClast and AUCinf were 1.00 (90% CI: 0.915– 1.099) and 1.00 (90% CI: 0.907–1.096), respectively. Maximum blood/plasma concentration (Cmax) was slightly (18%) higher for the granule formulation (geometric mean ratio 1.18; 90% CI 1.050–

Protocol No., Study Dates, Countries & Publication References	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 secondary objective was to evaluate the dose PK with the granule formulation, and To evaluate the safety and tolerability of deferasirox new granule formulation in comparison to the reference deferasirox (Exjade) formulation To evaluate the dose-proportionality of deferasirox pharmacokinetics with the granule formulation **population:** The study included a homogeneous population of healthy subjects who were treated under fasted conditions. **evaluations:** pharmacokinetics (PK): Plasma deferasirox concentrations were determined on Days 1 to 4, Days 8 to 11, Days 15 to 18, and Days 22 to 25 at the following time points: 0 (predose),		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 duration of the study for an individual subject was approximately 10 weeks with an additional screening time of a maximum of 14 days. 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. There were a total of	1.323).AUC was considered to across the three dose levels and Cmax was considered approximately dose proportional between 400 and 1200 mg single doses tested in healthy subjects.The safety data observed during the study were consistent with the known safety profile of deferasirox.

Protocol No., Study Dates, Countries & Publication References	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
	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 (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 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 electronic case report form (eCRF).		four treatment sequences for dosing. Dosing occurred on the first day of each treatment period for a total of 4 treatment periods. The first three treatment periods were seven days in duration, followed by the last treatment period of four days. Periods 1, 2, and 3 had a 6-day washout between each dose. 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 Day 55. **dosing**: Subjects were to ingest three 500 mg DTs of investigational product dissolved in 200 mL of	

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			water. For investigational product (400 mg, 800 mg and 1200 mg granules), the Investigator or designee was to dissolve 1 ×, 2 ×, or 3 × 400 mg granules, respectively, into 200 mL of water in a glass. After ingestion, the glass was rinsed with an additional 40 mL of water and the subject ingested the full contents of the glass. Thus, a total of 240 mL of water was ingested with each dose.	

Protocol No., Study Dates, Countries & Publication References	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:[CICL670F2105] **countries:** USA **start:** 29-Jul-2013 **end:** 02-Dec-2013 **publ.:** None	**design, goal & population:** **design:** A randomized, open-label, single-center, phase I, two-way, cross-over study to evaluate the pharmacokinetic comparability of deferasirox new granule formulation with the reference dispersible formulation in healthy subjects. **goal:** The primary objective was to evaluate pharmacokinetic (PK) comparability of a reduced dose of the deferasirox granule formulation given with a small amount of a soft food matrix (apple sauce) versus the reference dispersible tablet (DT) formulation of deferasirox under fasted conditions in healthy subjects. Secondary objective was to evaluate the safety and tolerability of deferasirox	**total:** 53(25w,23b,5o) **age:**18-52(30.6) **groups:** Group 1 (6m6f) Group 2 (9m,12f) Group 3 (13m,7f)	**form(s):** granular **duration:** 8 weeks with an additional screening time of a maximum of 14 days. **doses:** Group 1: No sequence Group 2: Treatment A: Single dose of 1200 mg of deferasirox granule formulation (3 stick packs of 400 mg) with apple sauce under fasted conditions Group 3: Treatment B: Single dose of 1500 mg reference DT formulation of deferasirox under fasted conditions	**status:** final **report:** content final **report date:** 11-Apr-2014 **general results:** The study was unable to demonstrate PK comparability between a single dose of 1200 mg deferasirox granule formulation versus a single dose of 1500 mg marketed DT formulation. • An increase in AUCinf, AUClast, and Cmax by 19%, 22%, and 41% on average, respectively, was observed with administration of 1200 mg deferasirox granules compared to the reference 1500 mg deferasirox DT. • Even with the higher exposure, the safety findings in this single-dose healthy volunteer study do not raise any new signals for deferasirox.

Protocol No., Study Dates, Countries & Publication References	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
	granule formulation, in comparison to the reference DT formulation. **Pharmacokinetics**: The primary PK variables were AUClast, AUCinf, and Cmax; the secondary PK variables were Tmax, T1/2, and lambda_z. The PK parameters were derived by Phoenix WinNonlin (version 6.2) based on the linear trapezoidal method via non-compartmental methods. **Safety**: Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug. 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 electrocardiograms. Interpretation of the 12-lead ECG tracing was assessed			

Protocol No., Study Dates, Countries & Publication References	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
	by the Investigator, or designee, and documented in the electronic case report forms. Also in females of child-bearing potential, a pregnancy test was performed, by the site on a serum sample obtained at baseline visit. Urine pregnancy test was done at the Screening, End Of the Treatment Visit and End Of the Study Visits.			

Protocol No., Study Dates, Countries & Publication References	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: [CICL670F2106] **countries:** USA **start:** 14-Sep-2012 **end:** 21-Dec-2012 **publ.:** None	**design, goal & population:** **design:** A single-center, open-label, randomized, two arms, cross-over study to investigate the effect of food on the pharmacokinetics of new deferasirox granule formulation in healthy subjects **goal:** **Primary:** Evaluate the effect of food on the pharmacokinetics (PK) of deferasirox granule formulation administered under fasted conditions (taken with water) and mixed with apple sauce or yogurt. Evaluate the effect of food on the PK of deferasirox granule formulation administered under fasted conditions (taken with water) and after low-fat breakfast or high-fat breakfast. **Secondary:** evaluate the safety and tolerability of deferasirox granule formulation in healthy subjects under fasted and fed conditions.	**total:** 63 arm 1: (28w,6b,1o) arm 2: (20w,8b) **age:** arm 1: 19-55(32.49) arm 2: 20-52 (33.86) **Groups 2** Arm 1: (22m,13f) Arm 2: (21m,7f)	**form(s):** granule formulation **duration:** 9 weeks with an additional screening time of a maximum of 14 days **doses:** Subjects were randomly assigned to one of the six Treatment Sequences either in Arm 1 or Arm 2 in a ratio of 1:1:1:1:1:1. The randomization was not stratified. Each Arm contained three Treatment Periods, namely Treatment Periods 1, 2 and 3. Treatment Periods 1 and 2 were 9 days in length while the last, Treatment Period 3, was only 4 days in length. Both Arm 1 and Arm 2 administered Treatment A; a single dose of 1200 mg deferasirox granules under fasting conditions. Arm 1 also included Treatment B; a	**status:** final **report:** content final **report date:** 26-Nov-2013 **general results:** There were no clinically relevant changes in deferasirox PK exposure when the granule formulation of deferasirox was administered with food. A single oral dose of 1200 mg deferasirox granules administered with soft foods demonstrated a lack of food effect with the amount of soft food used, i.e. 3 tablespoons of apple sauce or yogurt.

Protocol No., Study Dates, Countries & Publication References	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
			single dose of 1200 mg deferasirox granules with apple sauce and Treatment C; a single dose of 1200 mg deferasirox granules with yogurt. Arm 2 also included Treatment D; a single dose of 1200 mg deferasirox granules after a low-fat breakfast and Treatment E; a single dose of 1200 mg deferasirox granules after a high-fat breakfast. Each treatment was administered only once during the entire study in the order of assigned treatment sequence.There were approximately 18 evaluable subjects in each arm (three subjects per Sequence), i.e., a total of 36 evaluable subjects.	

protocol: [ICL670F1102 Part 1] **countries:** Japan **start:** 27-Jun-2014 **end:** 28-Sep-2014 **publ.:** None	**design, goal & population:** **design:** A randomized, open label, six sequences, cross-over study in healthy Japanese subjects to evaluate the pharmacokinetic comparability of deferasirox granule formulation with the reference dispersible tablet formulation (Exjade) **goal:** The primary objective was to evaluate the PK comparability of two different doses of the deferasirox granule formulation in comparison to the reference dispersible formulation (Exjade®) in healthy	total: 97 (97a) age:20-45 (29.6) groups:6 Group 1 (16m1f) Group 2 (15m,1f) Group 3 (15m.1f) Group 4 (15m.1f) Group 5 (15m,1f) Group 6 (15m,1f)	**form(s):** oral tablets **duration:** Each of the three treatment periods lasted nine days with an 8-day washout between the treatment periods. The total duration of the study for an individual subject was approximately 52 - 79 days with a screening time of a maximum of 27 days. **doses:** Treatment A: single dose of 1500 mg reference dispersible tablet (DT) formulation	**status:**final **report:**content final **report date:** 27-Nov-2014 **general results:** Exposure (AUClast and AUCinf) equivalence was demonstrated between both single dose of 990 mg or 1080 mg deferasirox granule formulation and single dose of 1500 mg deferasirox DT. Although AUClast and AUCinf were 10% higher in the 1080 mg granule treatment compared to the DT treatment, the 90% CI of the ratios was within the bioequivalence acceptance criteria of 80-125%. Cmax of 990 mg or 1080 mg

Protocol No., Study Dates, Countries & Publication References	**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**
	Japanese subjects under fasted conditions. The secondary objective was to evaluate the safety and tolerability of two different doses of the deferasirox granule formulation in comparison to the reference dispersible formulation (Exjade®) in healthy Japanese subjects under fasted conditions. **Population studied:** Healthy Japanese subjects **evaluations** **Efficacy**: The primary PK variables were AUClast, AUCinf, and Cmax; the secondary PK variables were Tmax, T1/2, MRTlast and lambda_z. The PK parameters were derived by Phoenix WinNonlin (version 6.2) based on the linear trapezoidal method via non-compartmental methods. **Safety**: Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity		of deferasirox (500 mg x 3 tablets) for oral suspension under fasted conditions Treatment B: single dose of 1080 mg of deferasirox granule formulation (90 mg x 12 stick packs) administered under fasted conditions Treatment C: single dose of 990 mg of deferasirox granule formulation (90 mg x 11 stick packs) administered under fasted conditions	deferasirox granule was 24% (90% CI: 1.1872-1.3019).and 34% (90% CI: 1.2794-1.4030) higher compared to the 1500 mg DT treatment. Although the 90% CI of the ratios was outside the bioequivalence acceptance criteria of 80-125%, the increased Cmax observed with deferasirox granules is not expected to have a clinically meaningful impact on either efficacy or safety. The safety findings in this single-dose healthy volunteer study do not raise any new signals for deferasirox. :

Protocol No., Study Dates, Countries & Publication References	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
	and relationship to study drug. 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 electrocardiograms. Interpretation of the 12-lead ECG tracing was assessed by the Investigator, or designee, and documented in the electronic case report forms			
protocol: [ICL670F1102 Part 2] **countries:** Japan **start:** 22-Apr-2015 **end:** 10-Aug-2015 **publ.:** None	**design, goal & population** **design:** A randomized, open label, six sequences, cross-over study in healthy Japanese subjects to evaluate the pharmacokinetic comparability of deferasirox granule formulation with the reference dispersible tablet formulation (Exjade®) **goal:** To evaluate the PK comparability of 900 mg DFX granule formulation in comparison to the reference dispersible formulation (1500	total: 96 (96a) age: 20-45 (31.5) groups: 2 (96m) Group 1: 48 subjects Group 2: 48 subjects	**form:** dispersible tablet, granule formulation **duration:** screening 27 days **doses:** Group 1: Treatment D: Single dose of 1500 mg reference dispersible tablet formulation of deferasirox (500 mg x 3 tablets) for oral suspension under fasted conditions Treatment E: Single dose of 900 mg of	**status:** final **report:** content final **report date:** 15-Dec-2015 **general results:** Exposure (AUClast and AUCinf) comparability was demonstrated between single dose of 900 mg DFX granule formulation and single dose of 1500 mg DFX DT as the 90% CI of the ratios was within the equivalence acceptance criteria of 80%-125%. Cmax of 900 mg DFX granule was 19% (90% CI: 1.1382, 1.2431) higher

Protocol No., Study Dates, Countries & Publication References	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
	mg) in healthy Japanese subjects under fasted conditions Secondary: To evaluate the safety and tolerability of 900 mg DFX granule formulation in comparison to the reference dispersible formulation (1500 mg) in healthy Japanese subjects under fasted conditions **Population studied:** Healthy Japanese subjects. **evaluations** **Pharmacokinetics:** The primary variables of the study were area under the concentration-time curve from zero to last timepoint and zero to infinity (AUClast and AUCinf, respectively) and maximum plasma concentration (Cmax). The secondary variables of the study were maximum plasma concentration time (Tmax), elimination half-life (T1/2), mean residence time from the time of dosing to the last timepoint (MRTlast) and terminal slope of elimination		deferasirox granule formulation (90 mg x 10 stick packs) administered under fasted conditions Group 2: Treatment E: Single dose of 900 mg of deferasirox granule formulation (90 mg x 10 stick packs) administered under fasted conditions. Treatment D: Single dose of 1500 mg reference dispersible tablet formulation of deferasirox (500 mg x 3 tablets) for oral suspension under fasted conditions	compared to the 1500 mg DT treatment, but comparability was proved because the 90% CI of the ratios was within the equivalence acceptance criteria of 80%-125%. The increased Cmax is not expected to have a clinically meaningful impact on either efficacy or safety [ICL670A2409 PK/PD analysis]. Furthermore, the 19% increase is not considered as clinically relevant considering the inter-individual variability of DFX PK observed in clinical studies. The overall concentration-time profiles of DFX were quite similar between DFX granule formulation and DFX DT, as reflected in similar Tmax, T1/2, MRTlast and lambda_z, and indicate that the formulation does not affect disposition of DFX. AUC in the new granule formulation exhibited less variability compared with that observed with the DT (CV% geo-mean was 29.2% vs. 32.8% for AUCinf and 27.1% vs. 31.4%

Protocol No., Study Dates, Countries & Publication References	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
	phase (Lambda_z). **Safety:** Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of hematology, blood chemistry, iron levels (at Screening visit only) and urinalysis performed at local laboratory and regular assessments of vital signs, physical condition, body weight and electrocardiogram (ECG). Interpretation of the 12-lead ECG tracing was assessed by the qualified physician, and documented in the ECG CRF page.			for AUClast), while inter subject variability in Cmax was similar between DFX granules and DFX DT (25.7% vs. 26.3%). Since AUC largely corresponds to efficacy and safety of DFX, the new granule formulation with less variability in AUC would have benefits in clinical settings. The safety data observed during the study were within the known safety profile as described in the current labeling for DFX.

Sponsor's table NDA 207968 section 5.2 Tabular list of Clinical Studies pages 4-16

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 Sprinkle (NDA 207968) focuses on the available safety information from studies F2104, F2105, F2106 and F1102. Note that the sponsor cross references the safety and efficacy of Exjade in NDA 21882 to support the current application for Jadenu Sprinkle NDA 207968. 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 21882 submission 000) and January 9, 2013 (NDA 21882 supplement 15), respectively.

5.3 Discussion of Individual Studies

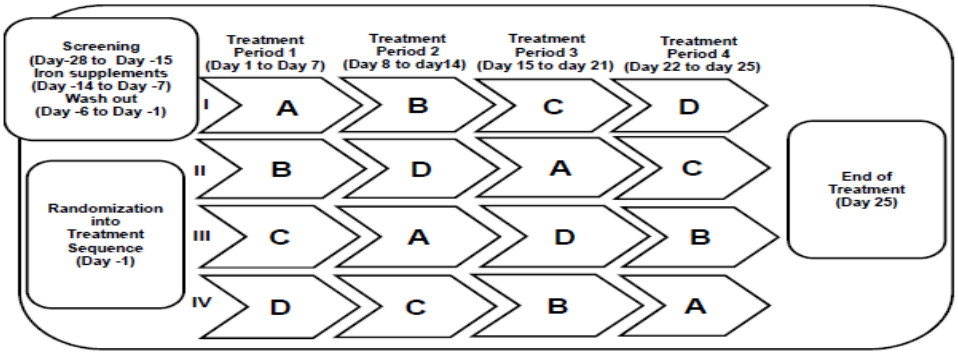
Studies supporting the Jadenu Sprinkle application NDA 207968 are described in section 5.1 Table of Studies in this review, i.e., studies F2104, F2105, F2106 and F1102. The following is a brief discussion of these four studies.

- F2104

  This was a randomized (1:1:1:1), open-label, single-center, four-period, four-sequence, crossover, single dose, Phase 1 bioavailability study with the deferasirox granule formulation, i.e., Jadenu Sprinkle, compared to the marketed reference formulation, i.e., Exjade (n=20 normal healthy subjects). The objective of this study was to evaluate the bioavailability of the deferasirox granule formulation at doses of 400mg, 800mg and 1200mg compared to the reference

deferasirox dispersible tablet formulation 1500mg administered orally once. Iron 325mg orally for eight days followed by a six day washout period was administered prior to deferasirox treatment. Deferasirox was administered on days 1, 8, 15 and 22. Plasma deferasirox concentrations were evaluated on Days 1-4, Days 8-11, Days 15-18 and Days 22-25. 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 F2104 Flow Chart

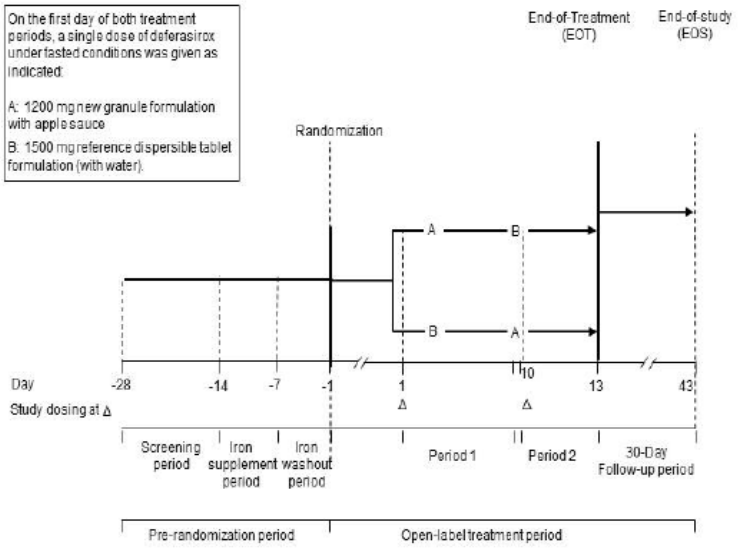


A, B, C. D = treatment periods for different deferasriox doses. Sponsor's figure Study Report CICL670F2104 page 364

- F2105

This was a randomized (1:1), open-label, single-center, two way, crossover, single dose, Phase 1 study in healthy adult subjects to demonstrate the pharmacokinetic (PK) comparability of deferasirox granule formulation compared to the reference deferasirox formulation tablet for oral suspension (n=41 normal healthy subjects). The primary objective was to evaluate the PK comparability of deferasirox dispersible tablet formulation to a reduced dosage strength of the deferasirox granule formulation, i.e., deferasirox dispersible tablet 1500mg dose compared to a deferasirox granule formulation 1200mg dose. Prior to deferasirox treatment subjects received iron 325mg administered orally once daily for eight days followed by a 6 day washout period. Plasma deferasirox concentrations were evaluated on Days 1-4 and Days 10-13. 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 F2105 Flow Chart

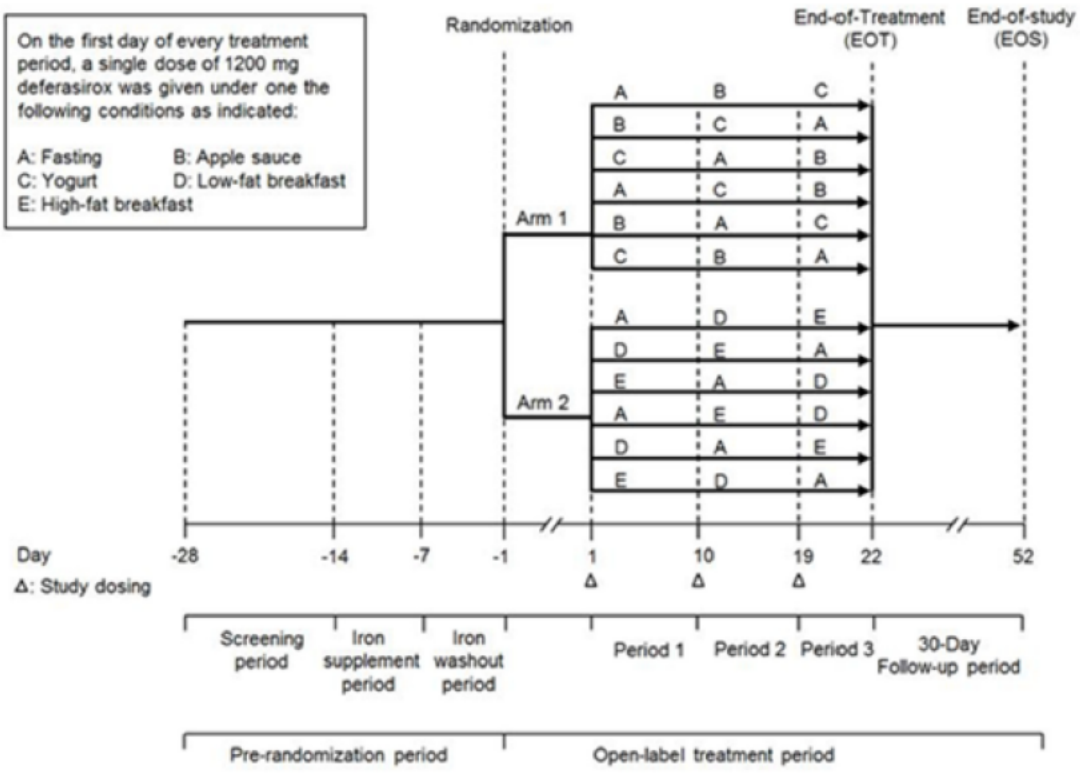


Sponsor's figure Study Report CICL670F2105 page 22

- F2106

  This was a single-center, open-label, randomized (1:1), two arm, cross-over, Phase 1 study evaluating the effect of food on deferasirox pharmacokinetics in healthy adult subjects (n=48 normal healthy subjects). The primary objective was to evaluate the effect of food on the PK of deferasirox granule formulation 1200mg administered orally once under fasted conditions and with a low-fat and a high-fat breakfast. Iron 325mg administered orally once daily was given for 8 days prior to deferasirox granule administration followed by a 6-day washout period. 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). Clinical laboratories that were evaluated with each period included hematologic, hepatic and renal function tests. The study flow chart is shown in the sponsor's figure below.

Figure 4. Study F2106 Flow Chart

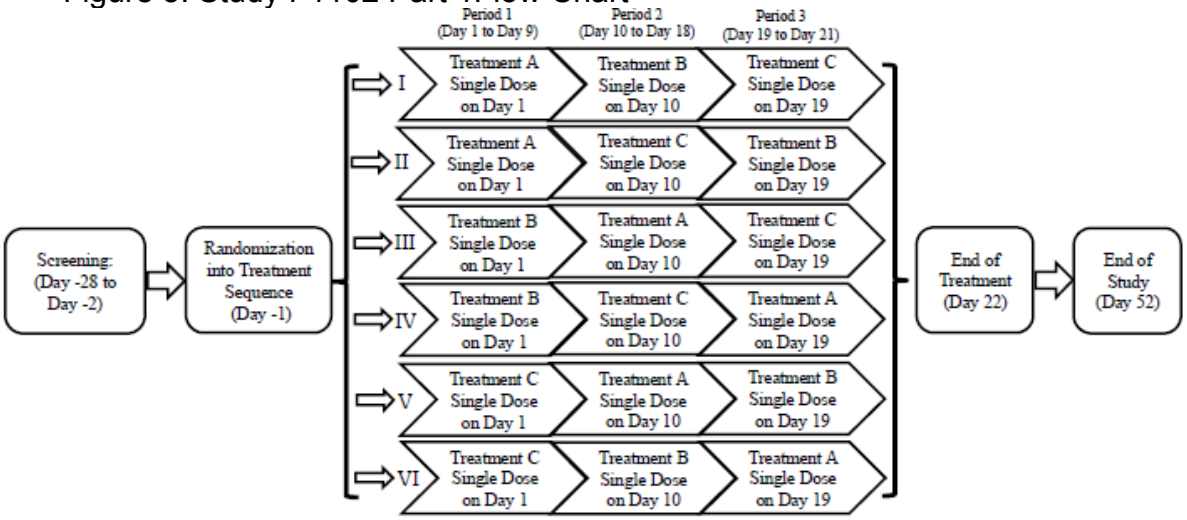


Sponsor's figure Study Report CICL670F2106 page 26

- F1102

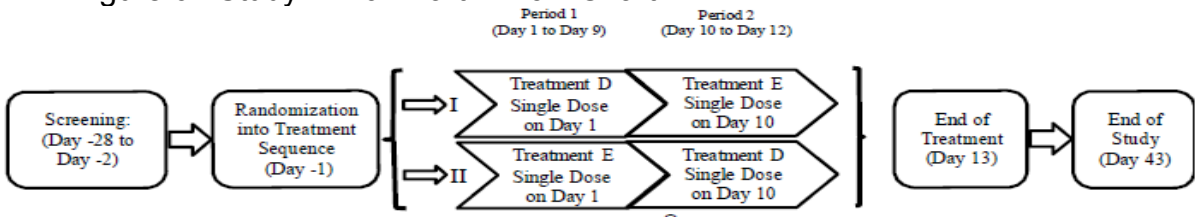
Study F1102 was a two part PK study conducted in Japan. Part 1 of the study was an open label, randomized (1:1:1:1:1:1), six sequence, crossover design that compared the PK of deferasirox granules 1080mg or 990mg administered orally once to the reference deferasirox product (Exjade, deferasirox tablet for oral suspension) 1500mg administered orally once in 97 healthy volunteers. Part 2 of the study was an open label, randomized (1:1), six sequence, crossover design that compared the PK of deferasirox granules 900mg administered orally once to the reference deferasirox formulation (Exjade) 1500mg administered orally once in 95 healthy volunteers. Iron 325mg administered orally once daily was supplemented for 8 days prior to deferasirox granule administration followed by a 6-day washout period. Plasma deferasirox concentrations were evaluated on days 1, 10 and 19. Safety assessments consisted of collecting all AEs, serious adverse events (SAEs). The study flow charts for parts 1 and 2 of the study are shown in the sponsor's figures below.

Figure 5. Study F1102 Part 1Flow Chart



Sponsor's figure Study Report ICL670F1102 Part 1 page 22

Figure 6. Study F1102 Part 2 Flow Chart



Sponsor's figure Study Report ICL670F1102 Part 2 page 21

Reviewer comment for section 5. From a clinical perspective the studies supporting the Jadenu application NDA 207968, i.e., F2104, F2105 and F2106 and F1102 appear to be reasonably well designed to support a bioavailability and bioequivalence comparison of Jadenu Sprinkle (deferasirox granules) to the reference product Exjade (deferasirox tablet for oral suspension). 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. The Clinical Pharmacology review by Dr. Sriram Subramaniam, final signature date April 13, 2017 states there is sufficient clinical pharmacology information provided in this NDA to support an approval recommendation. I agree with Dr. Subramaniam's review.

6 Review of Clinical Efficacy

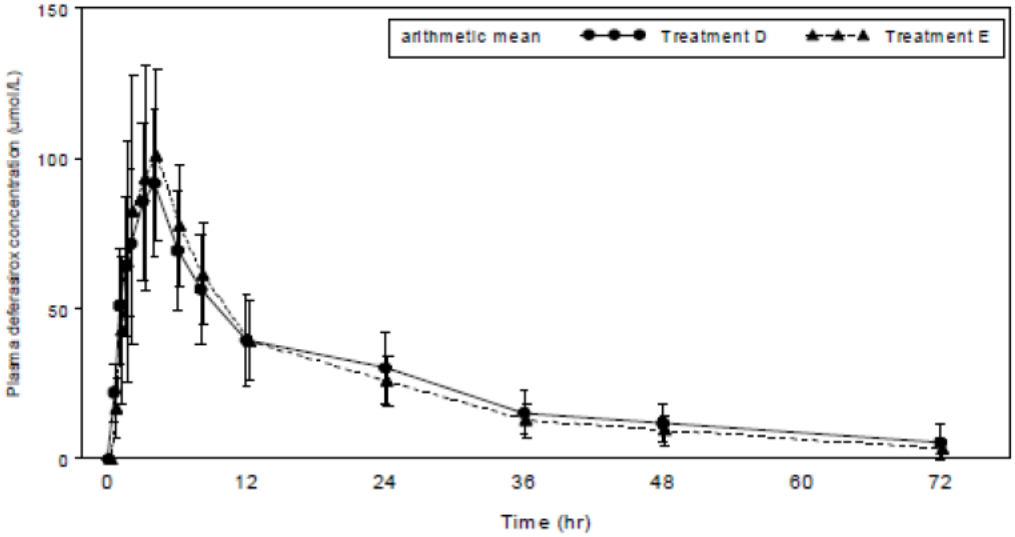
In NDA 207968 supporting document 1 letter date July 21, 2016 the sponsor proposes that Jadenu Sprinkle is indicated for the same indications as Exjade and Jadenu, i.e.,

- Jadenu Sprinkle 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) (b) (4).

- Jadenu Sprinkle 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. (b) (4) (b) (4).

The clinical pharmacology data for this application was reviewed by Dr. Sriram Subramaniam (Pharmacology Reviewer in the Division of Clinical Pharmacology V, final signature date April 13, 2017). An example of the plasma deferasirox concentration-time profile observed in study F1102 part 2 is shown in the sponsor's figure below. The sponsor states that the concentration-time profiles after a single oral dose of either the reference deferasirox product (Exjade, treatment D 1500mg in the figure below) or deferasirox granules (Jadenu Sprinkle, treatment E 900mg in the figure below) were generally comparable.

Figure 7. Mean (SD) Plasma Deferasirox Concentration-Time Profile in Study F1102 Part 2



- Treatment D = deferasirox tablet for oral suspension (Exjade) 1500mg administered orally once. Δ Treatment E= deferasirox granules (Jadenu Sprinkle) 900mg administered orally once. Sponsor's figure Study Report ICL670F1102 Part 2 page 50

The bioavailability, i.e., area under the curve (AUC) of deferasirox granules (Jadenu Sprinkle) was 52% greater than with deferasirox tablets for oral suspension (Exjade).

Overall, after strength-adjustment 1080mg of Jadenu Sprinkle was equivalent to 1500 mg of Exjade (deferasirox tablets for oral suspension) with respect to the mean AUC under fasting conditions. However, the mean Cmax was increased by 34% (90% confidence interval (CI): 1.3, 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 (see Clinical Pharmacology Review by Dr. Sriram Subramaniam for NDA 207968 final signature date April 13, 2017). Notably, in bioavailability studies submitted to support the application of Jadenu (deferasirox film coated tablets, NDA 206910) that compared the AUC and Cmax of Jadenu to the Cmax was 30% (90% CI: 1.2, 1.4) higher for Jadenu compared to Exjade. However, 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. Therefore, the 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 (see Clinical Pharmacology Review by Dr. Vicky Hsu for NDA 206910 final signature date February 3, 2015). The difference of 4% in Cmax in Jadenu Sprinkle compared to Jadenu is not clinically significant.

Reviewer comment for section 6. The sponsor cross references the efficacy of Exjade in NDA 21-882 to support the current application for Jadenu Sprinkle NDA 207968. 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 Sprinkle was 52% greater compared to Exjade. In bioavailability studies submitted to support the application of Jadenu (deferasirox film coated tablets, NDA 206910) that compared the AUC and Cmax of Jadenu to the Cmax was 30% (90% CI: 1.2, 1.4) higher for Jadenu compared to Exjade. However, 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. 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 Sprinkle starting dose compared to Exjade. The proposed starting dose of Jadenu Sprinkle is the same as that recommended for Jadenu. Also, proposed dose adjustments for Jadenu Sprinkle, Jadenu and Exjade during treatment are the same and are based on responses in serum ferritin and LIC. The Clinical Pharmacology review by Dr. Sriram Subramaniam final signature date April 13, 2017 states that the Division of Clinical Pharmacology V 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 F2104, F2105, F2106 and F1102 discussed in section 5 Sources of Clinical Data were reviewed to evaluate the safety of Jadenu in the application NDA 207968.

7.1.2 Categorization of Adverse Events

Adverse events (AEs) were characterized according to Medical Dictionary for Regulatory Activities (MedDRA) v. 15 terminology in studies F2104 and F2106 and MedDRA v. 16 terminology in studies F2105 and F1102.

7.2 Adequacy of Safety Assessments

Overall 320 adult healthy subjects (n=271 males and n=49 females) ranging in age from 18-55 years were enrolled in the four crossover pharmacology studies.

7.3 Major Safety Results

7.3.1 Deaths

No subjects died in any of the four pharmacology studies, i.e., F2104, F2105, F2106 or F1102.

7.3.2 Nonfatal Serious Adverse Events

No study drug related serious adverse events (SAEs) were reported in study F2104, F2105, F2106 or F1102.

7.3.3 Dropouts and/or Discontinuations

In study F2106, one subject in Arm 2 permanently discontinued study drug due to AE (mild rash). In study F1102 part 1 there were two subjects had an AE (mild rash and mild serum alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) increase) leading to discontinuation of treatment. The case of the subject who was prematurely discontinued from study F1102 part 1 is described below.

- Subject 1001-00117: The subject was a healthy male age 25 years who was enrolled in study F1102 part 1. The subject was treated with deferasirox granules (Jadenu Sprinkle) 990mg administered orally once. On day 1 the

patient had liver transaminase levels within normal levels. On day 9 after deferasirox granule treatment the subject's serum ALT was 153U/L and serum AST was 413U/L. No elevation in serum total bilirubin was reported. The subject was discontinued from the study on day 9. The subjects ALT and AST levels returned to normal levels within 3 weeks of study drug administration.

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 (see Exjade product label approved under NDA 21882 on August 12, 2016). A similar Boxed Warning is contained in the Jadenu product label (see Jadenu product label approved under NDA 206910 on August 12, 2016). The sponsor proposes to include the same Boxed Warning in the Jadenu Sprinkle product label (NDA 207968). No AEs of these types were reported in studies F2104, F2105, F2106 or F1102.

7.4.1 Supportive Safety Results

The most common adverse events (AEs) reported ≥ 4 subjects in studies F2104, F2105, F2106 or F1102 are shown in the reviewer's table below. The table shows that overall diarrhea was the most common AE reported in these studies. Diarrhea was slightly more often reported in subjects following Jadenu Sprinkle (deferasirox granules) than in subjects following Exjade (deferasirox dispersible tablets).

Table 3. Most Common Adverse Events Reported in ≥ 4 Subjects in Studies F2104, F2104, F2105 and F1102

Adverse Event	**Granules 400mg N=20 (n)**	**Granules 800mg N=20 (n)**	**Granules 1200mg N=109 (n)**	**Granules 900mg/ 990mg/ 1080mg N=192 (n)**	**Total Subjects Granules N=341 (n, %)**	**Total Subjects Dispersible Tablet N=253 (n, %)**
Diarrhea	0	0	2	19	21, 6	11, 4
Headache	1	2	0	1	4, 1	3, 1
AST/ALT Increased	0	0	0	4	4, 1	1, <1

Reviewer table derived from sponsor's tables Clinical Study Report Summary of Clinical Safety pages 16-18

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 hematologic or renal function clinical laboratory tests for subjects enrolled in studies

F2104, F2105, F2106 or F1102. In four subjects who were treated with Jadenu Sprinkle (deferasirox granules) mild serum AST/ALT elevation was observed. One subject (#1001-00117) was discontinued from study F1102 due to increased liver transaminases. This case is discussed in section 7.3.3 Dropout and/or Discontinuations in this review. No elevation in serum total bilirubin was observed which would be consistent with Hy's Law hepatotoxicity.

7.4.3 Vital Signs and Electrocardiograms (ECGs)

No significant changes in vital signs or ECGs were reported during any treatment period in studies F2104, F2105, F2106 or F1102.

7.4.4 Immunogenicity

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

7.5 Additional Safety Evaluations

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

The sponsor requests a waiver of pediatric studies of Jadenu Sprinkle in patients age 0 to < 2 years with chronic iron overload due to blood transfusions on the basis that iron overload requiring treatment chelation is rare in patients below 2 years of age. The sponsor also requests a waiver of pediatric studies of Jadenu Sprinkle in patients age 0 to 9 years with chronic iron overload in patients with NTDT syndromes on the basis that studies in patients 0-9 years in the NTDT setting were impossible or highly impractical. Deferasirox was granted Orphan Drug Designation as follows.

- November 21, 2002 for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age or older.
- February 24, 2015 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 concentration (LIC) of at least 5 milligrams of iron per gram of liver dry weight (mg Fe/g dw) and serum ferritin greater than 300 mcg/L.

The request for waiver of pediatric studies for Exjade was reviewed by Dr. George Shashaty (IND 58554 final signature date October 28, 2013). The basis of the request for other ages was that the pediatric population from ages 10-16 has been studied in deferasirox clinical trials in both transfusion-dependent thalassemia and non-transfusion dependent thalassemia, and that the pediatric population from age 2-10 years has been studied in deferasirox clinical trials in transfusion-dependent thalassemia. In addition, studies in patients with transfusion-dependent anemias were conducted under an Orphan Designation and are therefore exempt from the requirements for pediatric

studies under the Pediatric Research Equity Act (PREA) (Orphan Designation 02-1610). In his review Dr. Shashaty states that a waiver from the need for pediatric studies in the requested age groups should be granted. An Advice/Information Request Letter was sent to the sponsor on December 30, 2013 in which the sponsor's waiver request was granted.

Reviewer comment for Section 7. Review of safety in the studies supporting the Jadenu Sprinkle application in NDA 207968, i.e., studies F2104, F2105, F2106 and F1102 does not raise new or additional safety concerns for Jadenu Sprinkle compared to the marketed Exjade product. These studies were conducted in normal healthy male and female subjects. A similar safety profile for Jadenu Sprinkle is expected compared to the approved Jadenu product. The safety labeling described in the Exjade product label is the same the safety labeling for the approved Jadenu product label and the proposed Jadenu Sprinkle product label. Jadenu Sprinkle is exempt from PREA requirements because of the deferasirox Orphan Designation. However, the existing Postmarketing Requirements (PMRs) and Postmarketing commitments (PMCs) for pediatric studies of deferasirox under NDA 21882 (Exjade) and NDA 206910 (Jadenu) should be completed and studies may be modified to allow use of the deferasirox granule formulation (Jadenu Sprinkle).

8 Postmarket Experience

There are no clinical data in actual patients with treated with Jadenu Sprinkle. In NDA 21882 supporting document 1058 letter date January 29, 2016 (received January 29, 2016) the sponsor submitted the completed study report for study CICL670A2411 titled, "A 5 Year Observational Study (Registry) of Children Aged 2 To <6 Years At Enrollment With Transfusional Hemosiderosis Treated With Deferasirox," in order to fulfill PMC 750-1 which was issued at the time of the marketing approval for Exjade on November 2, 2005. With the marketing approval of Jadenu on March 30, 2015 PMR 2888-1 was issued which has the same wording as PMC 750-1 for Exjade. The Clinical Review of the submission was completed by Dr. Andrew Dmytrijuk in the Division of Hematology Products (DHP) final signature date March 15, 2017. In his review Dr. Dmytrijuk concludes that the data submitted in the study report for study CICL670A2411continue to support a positive benefit-risk evaluation for deferasirox for the treatment of transfusional iron overload in patients age 2-<6 years.

Dr. Dmytrijuk also reviewed the following submissions to NDA 21882 for Exjade (see Clinical Review final signature date March 15, 2017.

- NDA 21882 Periodic Adverse Drug Experience Report (PADER) supporting document 1086 letter date December 20, 2016 (received December 20, 2016) covering the reporting period from November 1, 2015 to October 31, 2016.

- NDA 21882 Annual Report (AR) supporting document 1084 letter date December 15, 2016 (received December 15, 2016) covering the reporting period from November 2, 2015 to November 1, 2016.
- NDA 21882 AR supporting document 1052 letter date December 23, 2015 (received December 23, 2015) covering the reporting period from November 2, 2014 to November 1, 2015.
- NDA 21882 Periodic Safety Update Report (PSUR) supporting document 1050 letter date December 21, 2015 (received December 21, 2015) covering the reporting period from November 1, 2014 to October 31, 2015.
- NDA 21882 PSUR supporting document 985 letter date December 23, 2014 (received December 23, 2014) covering the reporting period from November 1, 2013 to October 31, 2014.

The sponsor estimates that the cumulative exposure to deferasirox since marketing approval November 2, 2005 is 335,128 patient-years in adults and children and the exposure to deferasirox is 6,582 patient-years in adults and children in the US and Canada based on marketing experience during the reporting interval, i.e., November 1, 2015 to October 31, 2016. In his review (final signature date March 15, 2017) Dr. Dmytrijuk states that the annual number of pediatric fatal cases has not changed greatly from year to year based on the information in the three deferasirox annual reports reviewed above (range 15 to 33 fatal pediatric cases in the US and Canada). Case report data is limited in terms of the quality of data that can be obtained based on the subjective and incomplete nature of the reports. The causes of death for patients with reported renal or hepatic toxicity were confounded by underlying disease and concomitant illness. Also, the exposure to deferasirox has also not changed significantly based on the information in the three deferasirox annual reports reviewed above (range 5226 to 6582 patient-years in adults and children). From the information provided in the annual reports it is not possible to determine the deferasirox exposure in pediatric patients alone.

Recently, a pediatric-focused safety review for deferasirox was presented at the Pediatric Advisory Committee (PAC) on September 16, 2015 due to a query about the possible role of deferasirox in a young pediatric patient who died. A brief summary of the case is as follows.

- FAERS Case # 10757530: The case concerns a female patient age 2 years 11months with a history of transfusional hemosiderosis due to beta-thalassemia associated with anemia. Prior to the patient's death she was diagnosed with respiratory syncytial virus (RSV) infection. The patient had been treated with deferasirox for 11 months for iron overload. The patient's reported Exjade dose was 375mg alternating with 250mg administered orally once daily. The patient's serum ferritin at the start of Exjade therapy was 1600µg/L. The patient's serum ferritin level two months prior to the event was 655µg/L. The patient developed an upper respiratory tract illness without fever starting 3 days prior to admission

> and she had decreased oral intake. Starting 24 hours before admission she developed diarrhea that was described as increasing in frequency and volume. She continued to take Exjade and her last dose was the morning of admission. Her family brought her for evaluation by her primary care provider due to the illness and because she was "not speaking or acting herself". In the emergency department the patients was assessed to have fever and was in shock. An arterial blood gas (ABG) showed metabolic acidosis (ABG pH 7.12, pCO2 33). Serum blood tests showed lactic acidosis (5.2mmol/L), hepatic and renal failure. A serum ammonia level was 280µmol/L initially and increased to 398µmol/L two hours later. The patient had a coagulopathy. The patient's prothrombin time (PT) was 20.2 seconds and the International Normalized Ratio (INR) was 2.1. The patient's serum creatinine was 1.2mg/dL (reported to be 0.36mg/dL two months earlier). A test for respiratory syncytial virus (RSV) was positive. Her treatments included intravenously (IV) administered fluids and IV administered vitamin K. The patient was undergoing evaluation for liver transplant. Testing for CMV and Hepatitis A, B, and C, Wilson disease and other metabolic disorders was negative. The patient developed respiratory failure and hypotension. Subsequently the patient developed cerebral edema with tonsillar herniation and died.

In his review (final signature date March 15, 2017) Dr. Dmytrijuk summarizes additional safety information regarding deferasirox from the FDA Briefing Document that was presented March 6, 2017 at the Pediatric Advisory Committee Meeting completed by Dr. Peter Waldron (Clinical Reviewer in the Division of Pharmacovigilance (DPV), final signature date February 17, 2017) and safety information from the Epidemiology Review completed by Dr. Kate Gelperin (Clinical Reviewer in the Division of Epidemiology (DEPI), final signature date December 21, 2016). Dr. Dmytrijuk states in his review that currently the approved Exjade (approved under NDA 21882 on August 12, 2016) and Jadenu (approved under NDA 206910 on August 12, 2016) product labels approved contain a Boxed Warning that warns prescribers of the potential for renal failure and hepatic failure with deferasirox therapy. The product labels also contain detailed information regarding these potential AEs in the Warnings and Precautions section as well as specific deferasirox dosing and monitoring recommendations for patients with baseline hepatic or renal impairment.

A number of PMRs were issued during the approval of Jadenu 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 March 30, 2015. Both indications remain under Accelerated Approval status. The following list summarizes the PMRs for Jadenu (NDA 206910) in the March 30, 2015 Accelerated Approval Letter. The reviewer comments below summarize the current status of these PMRs.

- PMR 2888-1 Establish a registry for children aged 2 to < 6 years to enroll approximately 200 patients receiving deferasirox and follow them for 5 years. Collect data at least monthly for renal function and blood pressure and yearly for growth and development, and analyze the data for adverse renal reactions and delayed growth and development. Submit your monitoring scheme for our review and comment.

  The timetable you submitted on March 27, 2015, states that you will conduct this study according to the following schedule:

  Final Report Submission: 02/2016

Reviewer comment: At the time of approval for Exjade (deferasirox tablet for oral suspension under NDA 21882), i.e., November 2, 2005, PMR 750-1 was issued. At the time of approval of Jadenu (deferasirox film coated tablet under NDA 206910), i.e., March 30, 2015, PMR 2888-1 (shown above) was issued. PMR 750-1 for Exjade has the same wording as PMR 2888-1 for Jadenu. The study report to fulfill PMR 750-1 for Exjade was submitted in NDA 21882 supporting document 1058 letter date January 29, 2016 (received January 29, 2016). The sponsor submitted the completed study report for study CICL670A2411 titled, "A 5 Year Observational Study (Registry) of Children Aged 2 to <6 Years at Enrollment with Transfusional Hemosiderosis Treated with Deferasirox." Clinical review of the study report was completed by Dr. Andrew Dmytrijuk in the Division of Hematology Products (DHP), final signature date March 15, 2017. However, the sponsor did not submit this study report as an NDA Supplement as described in the Exjade Accelerated Approval letter issued November 2, 2005 for Exjade. Therefore, the sponsor should resubmit the study as an NDA Supplement as instructed in the Accelerated Approval letter issued November 2, 2005 for Exjade.

- PMR 2888-2 Conduct a trial to assess the long-term efficacy and safety of 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.

  The timetable you submitted on March 27, 2015, states that you will conduct this study according to the following schedule:

  Trial Completion: 05/2019
  Final Report Submission: 11/2019

- PMR 2888-3 Conduct a trial to assess the long-term efficacy (and safety) of 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.

  The timetable you submitted on March 27, 2015, states that you will conduct this study according to the following schedule:

  Trial Completion: 05/2019
  Final Report Submission: 11/2019

- PMR 2888-4 Conduct a prospective, randomized trial in at least 210 patients with low to intermediate risk myelodysplastic syndromes (MDS) receiving deferasirox for transfusional iron overload (approximately 140 patients) or placebo (approximately 70 patients) to determine the efficacy and safety of deferasirox in this population. The trial will continue for 3 years from the date the last patient is enrolled.

  The timetable you submitted on March 27, 2015, states that you will conduct this study according to the following schedule:

  Trial Completion: 03/2018
  Final Report Submission: 09/2018

- PMR 2888-5 Conduct a study, using your established registry, to evaluate the risk of growth inhibition in children (aged 10 to <18 years old at enrollment) with NTDT and treated with deferasirox for documented iron overload. Follow at least 40 children for up to 5 years to assess and analyze the long-term safety of treatment with deferasirox, including an assessment of growth, compared to children on a regular transfusion program receiving deferasirox (based on historical data). Provide annual interim reports on enrollment and outcomes.

  The timetable you submitted on March 27, 2015, states that you will conduct this study according to the following schedule:

  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

- PMR 2888-6 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 deferasirox for documented iron overload related to multiple transfusions for myelodysplastic syndrome with anemia requiring transfusions. This study does not replace monitoring and reporting as required by regulations.

  The timetable you submitted on March 27, 2015, states that you will conduct this study according to the following schedule:

  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

- PMR 2888-7 Complete a study of long-term follow-up (3 years) in 150 patients with myelodysplastic syndromes (MDS) receiving deferasirox to evaluate safety (including cardiac, hepatic, endocrine and renal) and hematologic and clinical benefit of deferasirox in these patients.

  The timetable you submitted on March 27, 2015, states that you will conduct this study according to the following schedule:

  Final Report Submission: 12/2019

- PMR 2888-8 Conduct a trial to assess ocular toxicity in patients receiving deferasirox. 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 deferasirox initiation) and at six month intervals. At least 60 patients should complete 2 years of follow-up.

  The timetable you submitted on March 27, 2015, states that you will conduct this study according to the following schedule:

  Final Protocol submission: 10/2015
  Final Report Submission: 12/2019

- PMR 2888-9 Conduct a trial to assess the long-term safety of deferasirox in patients with NTDT by conducting a trial of 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 March 27, 2015, states that you will conduct this study according to the following schedule:

  Trial Completion: 05/2019
  Final Report Submission: 11/2019

Reviewer comment: With the exception of the study to fulfill PMR 2888-1 the remaining studies to fulfill PMRs 2888-2 through 2888-9 are ongoing.

Reviewer comment for Section 8: There is no clinical data available in actual patients who were treated with Jadenu Sprinkle. In NDA 21882 supporting document 1058 letter date January 29, 2016 (received January 29, 2016) the sponsor submitted the completed study report for study CICL670A2411 titled, "A 5 Year Observational Study (Registry) of Children Aged 2 To <6 Years At Enrollment With Transfusional Hemosiderosis Treated With Deferasirox," in order to fulfill PMC 750-1 which was issued at the time of the marketing approval for Exjade on November 2, 2005. The Clinical Review of the submission was completed by Dr. Andrew Dmytrijuk in the Division of Hematology Products (DHP) final signature date March 15, 2017.

In his review Dr. Dmytrijuk concludes that the data submitted in the study report for study CICL670A2411continue to support a positive benefit-risk evaluation for deferasirox for the treatment of transfusional iron overload in patients age 2-<6 years. The sponsor estimates that the cumulative exposure to deferasirox since marketing approval November 2, 2005 to October 31, 2016 is 335,128 patient-years in adults and children and the exposure to deferasirox is 6,582 patient-years in adults and children in the US and Canada. In his review (final signature date March 15, 2017) Dr. Dmytrijuk states that the number of pediatric fatal cases has not changed greatly from year to year based on the information in the three deferasirox annual reports covering the reporting period from November 2013 to October 2016 (range 15 to 33 fatal pediatric cases). Case report data is limited in terms of the quality of data that can be obtained based on the subjective and incomplete nature of the reports.

A number of PMRs were issued during the approval of Jadenu on March 30, 2015. PMRs which were issued during the approval of Exjade on November 2, 2005 and January 23, 2013 should also apply to Jadenu and Jadenu Sprinkle. However, those PMCs and PMRs that have been fulfilled for Exjade can also be considered fulfilled for Jadenu and Jadenu Sprinkle. Use of the deferasirox granule (Jadenu Sprinkle) formulation should be allowed in the Exjade and Jadenu PMR and PMC studies. The study report to fulfill PMR 2888-1 for Jadenu was submitted in NDA 21882 supporting

document 1058 letter date January 29, 2016 (received January 29, 2016) the sponsor submitted the completed study report for study CICL670A2411 in order to fulfill PMC 750-1 which was issued at the time of the marketing approval for Exjade on November 2, 2005. Clinical review of the study report was completed by Dr. Dmytrijuk, final signature date March 15, 2017. However, the sponsor did not submit this study report as an NDA Supplement as described in the Exjade Accelerated Approval letter issued November 2, 2005 for Exjade. Therefore, the sponsor should resubmit the study as an NDA Supplement as instructed in the Exjade Accelerated Approval letter issued November 2, 2005 for Exjade. PMRs 2888-2 through 2888-9 for Jadenu are ongoing.

APPEARS THIS WAY ON ORIGINAL

9 Appendices

9.1 Literature Review/References

In order to determine if there might be an increased risk of adverse reactions such as overchelation of body iron or other adverse reactions due to the increased bioavailability of Jadenu Sprinkle 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 (NDA 21882) and Jadenu (NDA 206910) product labels approved August 12, 2016, respectively. The Exjade and Jadenu product labels state 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 deferasirox. The Exjade and Jadenu product labels state, “In case of overdose, induce vomiting and employ gastric lavage.” The Exjade and Jadenu product labels state that for patients with transfusional iron overload, serum ferritin should be measured monthly to assess for possible overchelation of iron. If the serum ferritin falls below 500µg/L, physicians should consider interrupting deferasirox therapy, since overchelation may increase deferasirox toxicity. For patients with NTDT, physicians should 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. Deferasirox therapy should be interrupted when the LIC is less than 3 mg Fe/g dw. Serum ferritin should be measured monthly, and if the serum ferritin falls below 300µg/L, deferasirox therapy should be interrupted and a confirmatory LIC should be obtained. The Exjade, Jadenu and proposed Jadenu Sprinkle product labels contain the same description of cases where overdose of deferasirox occurred and contain the same monitoring recommendations.

Reviewer comment: The Exjade and proposed Jadenu Sprinkle product labels appear to adequately describe the risk of overdose and overchelation with deferasirox. The Jadenu product label also adequately describes 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 Sprinkle label attached below incorporates the labeling recommendations from FDA review divisions and my proposed recommendation to the sponsor. Key clinical labeling recommendations for the Jadenu Sprinkle product label are as follows.

- Sponsor's proposed wording addition (underlined) in section 2.3 Administration :

  - Do not take JADENU tablets with aluminum-containing antacid products [see Drug Interactions (7.1)]. For patients who have difficulty swallowing whole tablets, JADENU tablets may be crushed and mixed with soft foods (e.g., yogurt or apple sauce) immediately prior to use and administered orally. Commercial crushers with serrated surfaces should be avoided for crushing a single 90 mg tablet. The dose should be immediately and completely consumed and not stored for future use.

    [redacted] by sprinkling the full dose on soft food (e.g. yogurt or apple sauce) immediately prior to use and administered orally. JADENU granules should be taken once a day, preferably at the same time each day [redacted] Do not take JADENU granules with aluminum-containing antacid products [see Drug Interactions (7.1)].

    For patients who are currently on chelation therapy with Exjade tablets for oral suspension and converting to JADENU [redacted], the dose [redacted] should be about 30% lower, rounded to the nearest whole tablet or sachet. The table below provides additional information on dosing conversion to JADENU [redacted].

    Reviewer comment: The sponsor's proposed wording is acceptable from a clinical perspective.

- The sponsor proposes to add the wording, "Granules (white to almost white granules)," in the column heading JADENU Tablets (film coated blue oval tablets) in section 2.3 Administration.

  Reviewer comment: The sponsor's proposed wording is acceptable from a clinical perspective.

- The sponsor proposes to add the Jadenu Sprinkle 90mg, 180mg and 360mg sachet dose forms under section 3 Dosage Forms and Strengths in the product label.

Reviewer comment: The sponsor's proposed wording is acceptable from a clinical perspective.

- The sponsor proposes to add the following wording to section 5.6 Hypersensitivity, section 5.7 Skin Reactions, section 6.1 Clinical Trials Experience subsection Other Adverse Reactions and section 6.2 Post Marketing Experience to align the Jadenu Sprinkle product label with the Exjade product label. The sponsor's proposed wording additions are underlined and wording deletions are in strikethrough format.

  - 5.6 Hypersensitivity

    JADENU may cause serious hypersensitivity reactions (such as anaphylaxis and angioedema), with the onset of the reaction usually occurring within the first month of treatment [see Adverse Reactions (6.2)]. If reactions are severe, discontinue JADENU and institute appropriate medical intervention. JADENU is contraindicated in patients with known hypersensitivity to deferasirox products and should not be reintroduced in patients who have experienced previous hypersensitivity reactions on deferasirox products due to the risk of anaphylactic shock.

  - 5.7 Severe Skin Reactions

    Severe skin reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and erythema multiforme, have been reported during deferasirox therapy [see Adverse Reactions (6.2)]. The risk of other skin reactions including DRESS (drug reaction with eosinophilia and systemic symptoms) cannot be excluded. If severe skin reactions are (b) (4) (b) (4) is suspected, discontinue JADENU immediately and do not reintroduce JADENU therapy.

  - Other Adverse Reactions

    In the population of more than 5,000 patients with transfusional iron overload who have been treated with deferasirox during clinical trials, adverse reactions occurring in 0.1% to 1% of patients included gastritis, edema, sleep disorder, pigmentation disorder, dizziness, anxiety, maculopathy, cholelithiasis, pyrexia, fatigue (b) (4) laryngeal pain, (b) (4) cataract, hearing loss, gastrointestinal hemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, (b) (4) renal tubular disorder (b) (4) (Fanconi's syndrome), and acute pancreatitis (with and without underlying biliary conditions). Adverse reactions occurring in 0.01% to 0.1% of patients included optic neuritis, esophagitis, and erythema multiforme. Adverse reactions which most frequently led to dose interruption or dose adjustment during clinical trials

were rash, gastrointestinal disorders, infections, increased serum creatinine, and increased serum transaminases.

- 6.2 Postmarketing Experience

  The following adverse reactions have been spontaneously reported during post-approval use of deferasirox in the transfusional iron overload setting. Because these reactions are reported voluntarily from a population of uncertain size, in which patients may have received concomitant medication, it is not always possible to reliably estimate frequency or establish a causal relationship to drug exposure.

  Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome (SJS), leukocytoclastic vasculitis, urticaria, alopecia, toxic epidermal necrolysis (TEN)

  Immune system disorders: hypersensitivity reactions (including anaphylactic reaction (b) (4) and angioedema)

  Renal and urinary disorders: (b) (4) acute renal failure, tubulointerstitial nephritis

  Hepatobiliary disorders: hepatic failure

  Gastrointestinal disorders: (b) (4) gastrointestinal perforation

  Blood and lymphatic system disorders: worsening anemia

  Reviewer comment: The sponsor's proposed wording changes in section 5.6 Hypersensitivity, section 5.7 Skin Reactions, section 6.1 Clinical Trials Experience subsection Other Adverse Reactions and section 6.2 Post Marketing Experience are acceptable and align with the Exjade and Jadenu product label (see NDA 21882 Exjade product label and NDA 206910 Jadenu product label approved August 12, 2016). These wording changes for Exjade NDA 21882 and Jadenu NDA 206910 were reviewed previously by Dr. Dmytrijuk (final signature date July 20, 2016).

- The sponsor proposes to add the following wording under section 11 Description in the product label

  - JADENU granules contain 90 mg, 180 mg, or 360 mg deferasirox. Inactive ingredients include microcrystalline cellulose, crospovidone; povidone (K30), magnesium stearate, colloidal silicon dioxide, poloxamer.

Reviewer comment: The sponsor's proposed wording is acceptable from a clinical perspective. The wording should be reviewed by the CMC reviewer.

- The sponsor proposes to add a subsection titled granules to section 12.3 Pharmacokinetics in the product label. The sponsor proposed wording to be added is in underlined format.
    - Granules

(b) (4)

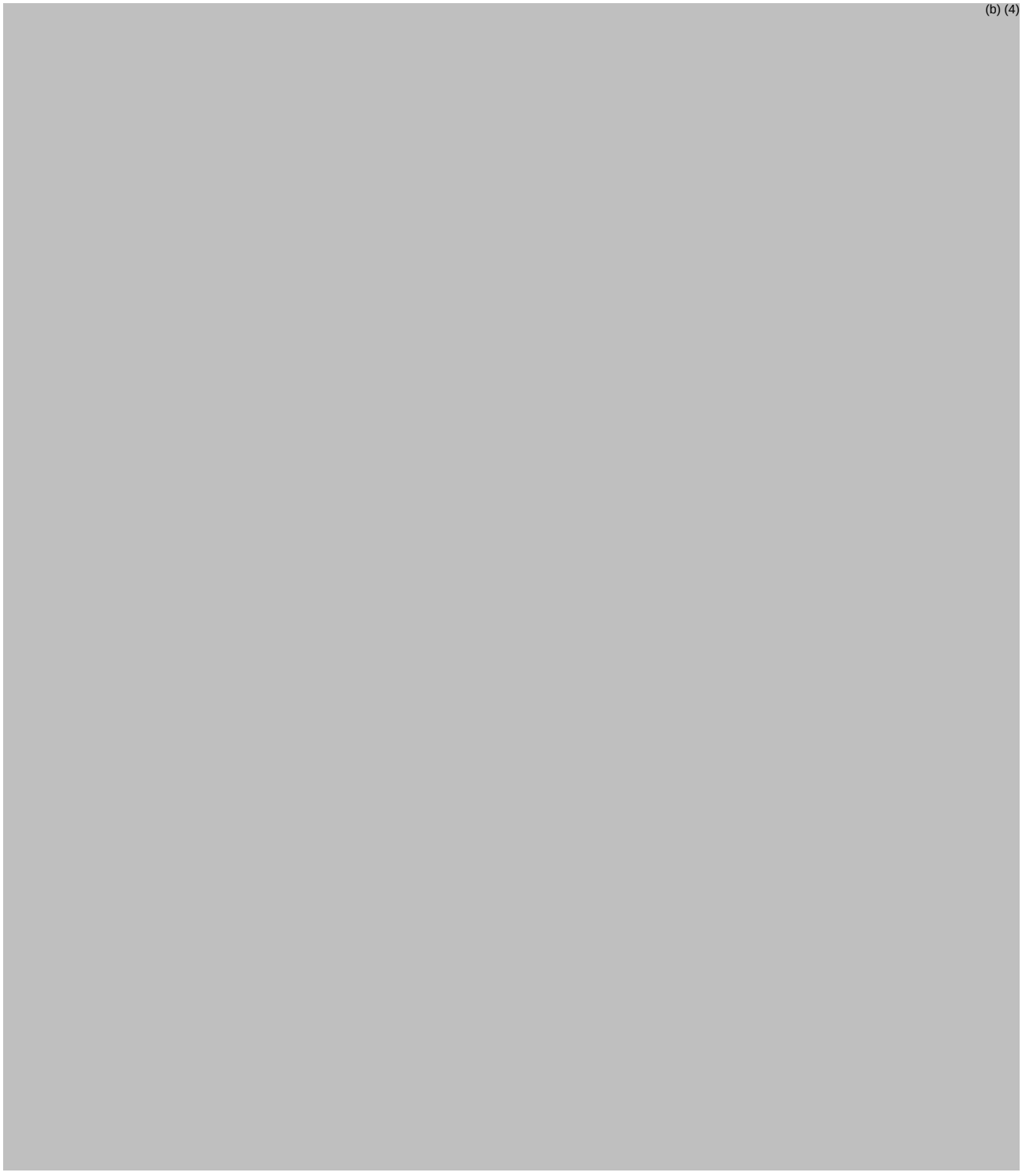
Reviewer comment: The sponsor's proposed wording is acceptable from a clinical perspective. The wording should be reviewed by the Clinical Pharmacology reviewer.

- The sponsor proposes to add the deferasirox granule (Jadenu Sprinkle) doseage forms to section 16 How Supplied/Storage and Handling section in the product label, i.e., 90mg, 180mg, 360mg. The sponsor also proposes to add wording regarding the proper storage temperature and conditions for the deferasirox granules.

  Reviewer comment: The sponsor's proposed wording is acceptable from a clinical perspective. The wording should be reviewed by the CMC reviewer.

- The sponsor proposes the following wording changes to section 17 Patient Counseling Information in the product label. The sponsor's proposed wording to be added is underlined and wording to be deleted is in strikethrough format.

(b) (4)



Reviewer comment: The proposed wording is acceptable from a clinical perspective. The draft Jadenu Sprinkle product label and reviewer comments to the sponsor attached below should be forwarded to the sponsor.

24 Pages 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
05/01/2017

KATHY M ROBIE SUH
05/01/2017