CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206910Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW-ADDENDUM **Division of Biopharmaceutics/Office of New Drug Products**			
Application No.:	206910	**Reviewer:** Banu Sizanli Zolnik, Ph.D.	
Division:	DHP	**Branch Chief (Acting):** Angelica Dorantes, Ph.D.	
Applicant:	Novartis	**Director (Acting)**: Paul Seo, Ph.D.	
Trade Name:	Jadenu™ Tablets	**Date Assigned:**	6/5/2014
Generic Name:	Deferasirox	**Date of Review:**	03/12/2015
Indication:	Treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older	**GRMP date**	02/23/2015
		PDUFA Date	03/30/2015
Formulation/strength	Tablets/ 90 mg, 180 mg and 360 mg	**Route of Administration**: Oral	
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission Dates Original NDA dated 05/30/2014 Amendment (SDN-011) dated 03/12/2015		**Date of informal/ Formal Consult**	
		OSI Consult Request dated 7/23/2014, for the Inspection of BE studies	
Type of Submission:	Original NDA 505 (b)(1)		
Key review points	• The evaluation and acceptability of the pivotal bioequivalence study F2102 supporting the approval of the proposed drug product, • The evaluation of the proposed dissolution method and acceptance criterion, and • The evaluation of the biowaiver request for the lower strengths.		

BIOPHARMACEUTICS EVALUATION

This document is an addendum to the original Biopharmaceutics review by Dr. Banu Zolnik uploaded in Panorama on March 23, 2015. The CR recommendation included in the Original Biopharmaceutics review is being revised in this review Addendum.

This addendum evaluates the following:

1) **Bioequivalence:**

   In the original Biopharmaceutics Review (dated 2/23/2015) a complete response was recommended because of failed bioequivalence results with respect to the Cmax metric as defined by the FDA's 80-125% criteria for bioequivalence. In the original review questions with the specific Biopharmaceutics concerns were listed. Therefore, during the NDA's wrap-up meeting, Biopharmaceutics asked if the concerns included in their review were shared by the clinical team. The Clinical Reviewer, Dr. Andrew Dmytrijuk responded that from the clinical perspective, there were no additional safety concerns with 30% higher Cmax values and reiterated that the higher Cmax values observed with Jadenu were within the overall range of those observed with Exjade in healthy subjects and patients. Also, Dr. Dmytrijuk mentioned that the provided exposure-response data for renal laboratory values were sufficient to support the overall safety of the product. Refer to Dr. Dmytrijuk's clinical review for specific details.

   In light of the clinical team perspective as noted above, such that the provided exposure-response data supporting the 30% higher rate of exposure are considered adequate, the Division of Biopharmaceutics original concerns are mitigated and agrees that the bioequivalence between the proposed Jadenu product and the listed Exjade product was demonstrated using a traditional 90% CI BE approach for AUC and an exposure-response approach for Cmax.

2) **Biowaiver Request:**

   In the original Biopharmaceutics review, the biowaiver request for the lower strengths was denied because of the lack of an acceptable in vivo BE study for the highest strength. However, since the lack of bioequivalence issue has been resolved, the biowaiver request for the lower 90 mg and 180 mg strengths is granted.

3) **Dissolution Testing:**

   On March 12, 2015, the Applicant submitted Amendment SDN-011 providing their concurrence to implement the FDA's recommended acceptance criterion of Q=(b)(4)% at 15 minutes for the dissolution test of Jadenu tablets. Amendment 011 also included the updated CMC corresponding sections with the revised criterion for the dissolution test.

The following dissolution method and acceptance criterion are found acceptable for QC (quality assurance) purposes for batch release and stability testing.

QC Dissolution Test for Jadenu Tablets, 90, 180, and 360 mg				
USP Apparatus	**Rotation Speed**	**Medium Volume**	**Medium/ Temperature**	**Acceptance Criterion**
USP II	75 rpm	900 mL	Phosphate Buffer pH 6.8 with 0.5% polysorbate 20 at 37 ± 0.5°C	Q= (b) (4)% at 15 min

II) RECOMMENDATION

From the Biopharmaceutics perspective, NDA 206910 for Jadenu (deferasirox) tablets is recommended for **APPROVAL.**

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BIOPHARMACEUTICS REVIEW **Division of Biopharmaceutics/Office of New Drug Products**			
Application No.:	206910	**Reviewer:** Banu Sizanli Zolnik, Ph.D.	
Division:	DHP	**Branch Chief (Acting):** Angelica Dorantes, Ph.D.	
Applicant:	Novartis	**Director (Acting)**: Paul Seo, Ph.D.	
Trade Name:	Jadenu™ Tablets[1]	**Date Assigned:**	6/5/2014
Generic Name:	Deferasirox	**Date of Review:**	2/23/2015
Indication:	Treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older	**GRMP date**	02/23/2015
		PDUFA Date	03/30/2015
Formulation/strength	Tablets/ 90 mg, 180 mg and 360 mg	**Route of Administration**: Oral	
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission Dates Seq. 000 dated 05/30/2014		**Date of informal/ Formal Consult** OSI Consult Request dated 7/23/2014, for the Inspection of BE studies	
Type of Submission:	Original NDA 505 (b)(1)		
Key review points	• The evaluation and acceptability of the pivotal bioequivalence study F2102 supporting the approval of the proposed drug product, • Evaluation of the bio-analytical method and method validation used for study F2102. • Audit/inspection reports of the BE study (clinical and bio-analytical sites). • The evaluation of the proposed dissolution method and acceptance criterion, and • The evaluation of the biowaiver request for the lower strengths.		

[1] Jadenu trade name is found conditionally acceptable (refer to communication dated 12/03/2014 by Kellie Taylor, Pharm.D, MPH, Office of Medication Error Prevention and Risk Management)

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I) SUMMARY OF IMPORTANT BIOPHARMACEUTICS FINDINGS

General:
Deferasirox is an iron chelator indicated for the treatment of chronic iron overload due to blood transfusions patients 2 years of age and older and for the treatment of chronic iron overload in patients 10 years of age and older with non-transfusion dependent thalassemia syndromes.

The proposed drug product, Jadenu (deferasirox) film-coated tablets (FCT), was developed by Novartis to overcome the palatability issues observed with their commercial drug product, Exjade (deferasirox) tablets for oral suspension (DP), approved by FDA under NDA 21882 on 11/2/2005.

The proposed drug product is an immediate tablet in the following strengths: 90, 180, and 360 mg for once daily administration and is dosed based on body weight.

Clinical Studies:
To support the approval of the proposed Jadenu deferasirox film coated tablets, the following studies were submitted;

- **Study F2101**, a pilot relative bioavailability study comparing the pharmacokinetics of the three uncoated tablet formulations of deferasirox to the currently available marketed DT formulation at 1500 mg dose to select a formulation for further development
- **Study F2102**, a pivotal single-dose fasted bioequivalence study conducted to evaluate the pharmacokinetics of the proposed deferasirox drug product (FCT, 1080 mg) to those of the listed drug product, Exjade tablets for oral suspension (DT, 1500 mg) using bioequivalence criteria
- **Study F2103**, a food effect study to assess the pharmacokinetics of deferasirox FCT when administered under fasting or fed conditions (low fat or high fat meal).
- (b) (4)
- **Study A2409 PK/PD analysis**, a post-hoc PK/PD analysis of a clinical study for the currently approved dispersible tablet (DT) formulation to determine the relative contributions of AUC and Cmax to the safety and efficacy profiles of deferasirox.

Study **F2102** is being evaluated in this Biopharmaceutics review. Studies **F2101** and (b) (4) were deemed NOT critical for review and (b) (4)

Studies **F2103** (food effect) and the post-hoc PK/PD analysis (**Study A2409)** were evaluated by the assigned Clinical Pharmacology Reviewers as per the division of review

responsibilities between Biopharmaceutics and Clinical Pharmacology. Refer to the OCP review dated 2/3/2015 in DARRTS.

Pivotal Bioequivalence

Pivotal study F2102 was conducted to demonstrate bioequivalence between the proposed deferasirox drug product (FCT) and the listed drug product, Exjade tablets for oral suspension (aka dispersible tablet formulation, DT). The results indicate lack of bioequivalence with respect pharmacokinetic parameter, Cmax. The rate of exposure represented by mean Cmax was 30% higher for the proposed Jadenu FCT product (90% CI: 120-140%). Therefore, bioequivalence was NOT satisfactorily demonstrated between the approved Exjade and the proposed Jadenu products.

Dissolution Method and Acceptance Criterion

The following dissolution method and acceptance criterion are been proposed for product quality assurance.

USP Apparatus	Rotation Speed	Medium Volume	Medium/ Temperature	Proposed Acceptance Criterion
USP II	75 rpm	900 mL	Phosphate Buffer pH 6.8 with 0.5% polysorbate 20 at 37 ± 0.5°C	Q= (b) (4) % at (b) (4) min

Although the proposed dissolution method is not discriminating, it is found acceptable for QC purposes. However, the proposed acceptance criterion of Q= (b) (4) % is not supported by the data and is NOT acceptable. The dissolution data support a criterion of Q = (b) (4) % at 15 minutes for Jadenu (deferasirox) film coated tablets and the Applicant will be requested to implement this criterion for batch release and stability testing.

Biowaiver Request

Since the biowaiver's requirement of an acceptable bioequivalence study for the highest strength was NOT met, the Applicant's biowaiver request is not fully supported and the biowaiver for the lower 90 and 180 mg strengths of Jadenu (deferasirox) film coated tablets is NOT granted.

II) RECOMMENDATION

The Division of Biopharmaceutics had evaluated the in vivo and in vitro biopharmaceutics information provided in NDA 206910 for Jadenu (deferasirox) film coated tablets and has the following comments:

Bioequivalence: The pivotal BE study F2102 failed bioequivalence with respect to Cmax (rate of exposure). To address the deviation from the FDA's 80-125% criteria for bioequivalence, the Applicant submitted a post-hoc PK/PD analysis in support of the safety of their proposed product. The data from this post-hoc analysis were evaluated by

the Office of Clinical Pharmacology (OCP). The OCP reviewing team agrees with the Applicant's conclusion that the higher Cmax values observed with the new Jadenu tablets are not expected to be clinically meaningful.

However, the Division of biopharmaceutics has the following remaining questions about the clinical and regulatory impact of the higher rate of exposure of the proposed drug product:

- Taking into account that Exjade was approved under the provisions of accelerated approval regulations (21 CFR 314.510) with very limited efficacy and safety data and 11 post-marketing study commitments (PMC), 2) have been several revisions to the labeling to address post-marketing safety concerns, and 3) to this date still there are pending clinical PMC addressing efficacy and safety concerns, **is it appropriate to use BE as a surrogate for efficacy and safety?**
- **Is it acceptable to deviate from the standard bioequivalence criteria?**
- **Is there a justified merit for this deviation?**
- **Is overcoming the palatability issue observed with the commercial drug product, Exjade, a justifiable reason to deviate from the standard BE criteria?**
- **Are there other clinical considerations that warrant the approval of the proposed Jadenu product?**
- **Can we assume that the renal laboratory values chosen for the exposure-response analysis represent the most critical safety signals?**
- **Can we assume that titration will mitigate the safety concerns of a 30% higher Cmax for Jadenu; when it did not happen for Exjade, which is also titrateable?**
- **Is it appropriate to introduce in the market a bio-inequivalent product, which in the future will serve as the reference listed product for 505b2 and generic submissions?**
- Considering that the FDA's overall mission is to protect the public health, **is it acceptable to introduce in the market a drug product with a higher rate of exposure (mean Cmax), which potentially can have a higher probability of adverse events or safety issues?**

Based on the above concerns, the Division of Biopharmaceutics considers that it is not warranted to deviate from the FDA's bioequivalence criteria and accept a drug product with a failed bioequivalence study. Therefore, the Division of Biopharmaceutics recommends that the approval of NDA 206910 be supported with an in vivo BE study demonstrating the bioequivalence of the Jadenu and Exjade products with respect to both metrics, Cmax and AUC (i.e., by reformulating the current Jadenu product).

Biowaiver Request:
The biowaiver request for the lower 90 and 180 mg strengths of Jadenu tablets cannot be granted at this time because of the lack of an acceptable in vivo BE study for the higher strength supporting this request.

Dissolution Acceptance Criterion: The proposed dissolution acceptance criterion of Q= (b) (4)% is not supported by the data and is NOT acceptable. The dissolution data support a (b) (4) Q = (b) (4)% at 15 minutes limit and the Applicant will be requested to implement this criterion for batch release and stability testing.

Overall Recommendation,

The Division of Biopharmaceutics has determined that the provided biopharmaceutics information do not to support an approval recommendation. Therefore, a **Complete Response** action is recommended for NDA 206910 for Jadenu (deferasirox) Tablets.

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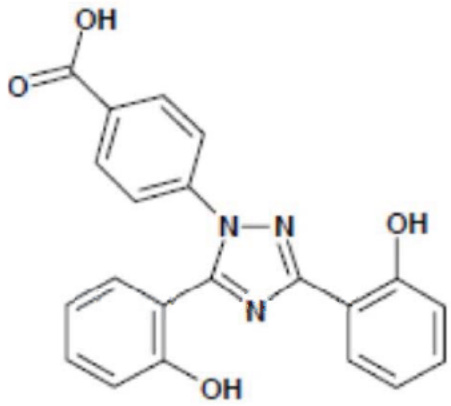
III) QUESTION BASED REVIEW – BIOPHARMACEUTICS EVALUATION

1. GENERAL ATTRIBUTES

1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?



Deferasirox is white to slightly yellow powder. (b) (4)

Drug Product

The proposed drug product is an immediate release film coated tablet. The composition information is shown below. There is an approved deferasirox tablets for oral suspension -Exjade 125 mg, 250 mg, and 360 mg on the market (NDA 21882, approval date: November 2, 2005). The proposed product is developed to overcome limitations of Exjade tablets such as dispersing the Exjade tablets in water or juice, and the need to rinse the insoluble residual drug with additional liquid to achieve the entire dose. Throughout the submission, Exjade, the reference formulation, is referred as dispersible tablet (DT) formulation.

Table. Composition of deferasirox tablets, 90 mg, 180 mg and 360 mg film coated tablet

Table 2-1 Composition of ICL670 90 mg, 180 mg and 360 mg film-coated tablet

Ingredient	Amount per 90 mg film-coated tablet (mg)	Amount per 180 mg film-coated tablet (mg)	Amount per 360 mg film-coated tablet (mg)	Function	Reference to standards
ICL670				(b) (4)	Novartis monograph
Microcrystalline cellulose (b) (4)					NF
(b) (4)					NF
Crospovidone					NF
Povidone K30					NF
Magnesium stearate[1]					NF
Colloidal silicon dioxide					NF
Poloxamer 188					NF
Core tablet Weight (mg)					
Coating[2]					
Opadry blue[2, 3] (b) (4)					Novartis Monograph USP
Total film-coated tablet weight (mg)					
(b) (4)					

Table. Composition information with percent active and excipient (w/w) of the total tablet weight (Calculated by the reviewer)

Ingredient	Amount per 90 mg tablet	% w/w	Amount per 180 mg tablet	% w/w	Amount per 360 mg tablet	% w/w
Deferasirox	90.00	(b) (4)	180.00	(b) (4)	360.00	(b) (4)
MCC (b) (4)						(b) (4)
(b) (4)						
Crospovidone						
Povidone K30						
Mg stearate						
Coll silicon dioxide						
Poloxomer 188						
Opadry Blue (b) (4)						

Reviewer's Comment:
The two lower strengths (30 mg and 180 mg) are proportionally similar in their active and inactive ingredients when they are compared to the higher strength (360 mg).

1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Deferasirox is an orally active chelator that is selective for iron (as $F2^{+3}$). (b) (4) The proposed indications for Jadenu Tablets are; 1) the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older and 2) the treatment of chronic iron overload in patients 10 years of age and older with 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.

1.3 What are the proposed dosage(s) and route(s) of administration?

Route of Administration: Oral
Strengths: 90, 180, 360 mg immediate release film-coated tablets
Dosing Regimen: In patients with transfusional iron overload: recommended initial dose is 14 mg/kg once daily. In patients with non-transfusion-dependent thalassemia (NTDT): recommended initial dose is 7 mg/kg once daily.

1.4 Is there any information on BCS classification? What claim did the Applicant make based on BCS classification? What data are available to support this claim?

Deferasirox is reported to be a BCS Class II drug substance (poorly soluble, highly permeable drug). Deferasirox is poorly soluble at low pH. At pH of 6.8 and 37^{o}C, its solubility is 0.04 mg/mL. The findings from a mass balance study indicate that approximately 90% of an orally administered dose of deferasirox is absorbed. In addition, deferasirox was shown to be highly permeable (intrinsic permeability > 80%) using human intestinal Caco-2 cell line.

2. GENERAL BIOPHARMACEUTICS (IN VIVO)

2.1 What are the biopharmaceutics studies provided to support the proposed to-be-marketed drug product?

To support the approval of the proposed Jadenu (deferasirox film coated tablets, the Applicant provided the following studies;

Table 1-1 Clinical studies included in the submission

Study no. / Type of study	Title	N	Deferasirox dose (form)	Food
[Study F2101] / pilot bioavailability study	A randomized, open-label, single-center, four-period, cross-over study evaluating the bioavailability of deferasirox (single dose) from three new formulations in comparison to the reference marketed deferasirox formulation in healthy subjects	20	1500mg (uncoated tablets) / 1500mg (DT)	fasted/ fasted
[Study F2102] / pivotal pharmacokinetic comparability study	A randomized, open-label, single-center, phase I, crossover study to evaluate the pharmacokinetic comparability of deferasirox new tablet formulation with the reference dispersible formulation in healthy subjects	32	1080mg (FCT) / 1500mg (DT)	fasted/ fasted
[Study F2103] / food effect study	A single-center, open-label, randomized, cross-over study to investigate the effect of food on the pharmacokinetics of new deferasirox tablet formulation in healthy subjects	25	1080mg (FCT)	fed/ fasted
(b) (4)				
[A2409 PK/PD analysis]	A one-year, open-label, single arm, multi-center trial evaluating the efficacy and safety of oral ICL670 (20 mg/kg/day) in patients diagnosed with transfusion-dependent iron overload: PK/PD analysis.	1744	20 mg/kg body weight/day (dispersible tablet formulation)	

DT= dispersible tablets (current formulation); FCT= film-coated tablets; (b) (4) N= number of subjects exposed to deferasirox; PK/PD: pharmacokinetic/pharmacodynamic

Study **F2102** is being evaluated in this Biopharmaceutics review. Studies **F2101** and (b) (4) were deemed NOT critical for review and (b) (4)

Studies **F2103** (food effect) and the post-hoc PK/PD analysis (**Study A2409)** were evaluated by the assigned Clinical Pharmacology Reviewers as per the division of review responsibilities between Biopharmaceutics and Clinical Pharmacology. Refer to the OCP review dated 2/3/2015 in DARRTS.

2.2 In vivo Bioequivalence Study F2102

To support the approval of the proposed product, the Applicant conducted Pivotal BE study F2102.

Study Title: "*A randomized, open label, single center, Phase 1, cross-over study to evaluate the pharmacokinetic comparability of deferasirox new tablet formulation with the reference dispersible formulation in healthy subjects*".

Study Objective:
The objective of the study was to evaluate PK comparability of deferasirox with the proposed film-coated formulation (FTC) vs. the reference Exjade tablets for oral

suspension (aka dispersible tablet formulation, DT) in healthy subjects under fasted conditions.

Study Design: Single dose, two-period, two-sequence cross over fasting study

Number of patients: 44 subjects enrolled, 34 subjects were treated, and 32 subjects completed the study treatments.

Test Product: Defarasirox film coated tablets, 1080 mg (360 mg X3),
Batch: AEUS/2012-0106
Reference Product: Exjade tablets, 1500 mg (500 mg X 3), Batch: S0325

Results:
The following tables present the summaries of the results and descriptive statistics for the primary and secondary pharmacokinetic variables for pivotal BE study F2102.

Table 11-4 Primary pharmacokinetic variables – descriptive statistics for AUClast, AUCinf, and Cmax by treatment (PAS)

Primary pharmacokinetics derived from plasma levels		FCT N=32	DT N=32
AUClast (µmol × h/L)	n	32	32
	Mean (SD)	1373.16 (603.31)	1411.76 (689.19)
	CV%	43.94	48.82
	Geometric mean	1273.78	1270.79
	CV% geometric mean	39.22	49.70
	Median	1193.38	1314.11
	Range	711.7–3417.8	337.2–3490.3
AUCinf (µmol × h/L)	n	32	32
	Mean (SD)	1409.05 (622.39)	1477.77 (726.69)
	CV%	44.17	49.17
	Geometric mean	1307.04	1327.01
	CV% geometric mean	39.15	50.29
	Median	1236.49	1347.24
	Range	729.0–3574.6	359.0–3559.9
Cmax (µmol/L)	n	32	32
	Mean (SD)	109.67 (30.30)	85.71 (27.31)
	CV%	27.63	31.86
	Geometric mean	105.83	81.54
	CV% geometric mean	27.54	33.35
	Median	104.50	88.00
	Range	65.0–197.0	36.2–153.0

FCT = Film-coated tablet: single dose of 1080-mg deferasirox oral film-coated tablets (3 tablets × 360 mg)
DT = Dispersible tablet/reference: single dose of 1500-mg deferasirox dispersible tablets for oral suspension (3 tablets × 500 mg)
Source: Table 14.2-2.1

Table 11-5 Secondary pharmacokinetic variables – descriptive statistics for Tmax, T1/2, and lambda_z by treatment (PAS)

Secondary pharmacokinetics derived from plasma levels		FCT N=32	DT N=32
Tmax (h)	N	32	32
	Median	2.00	3.00
	Range	1.50–6.03	1.00–8.00
T1/2 (h)	N	32	32
	Mean (SD)	13.039 (3.9603)	16.278 (4.7061)
	CV%	30.37	28.91
	Geometric mean	12.48	15.64
	CV% geometric mean	30.69	29.47
	Median	12.165	15.255
	Range	6.38–22.08	7.66–28.34
Lambda_z (h^{-1})	N	32	32
	Mean (SD)	0.058 (0.0174)	0.046 (0.0136)
	CV%	29.99	29.51
	Geometric mean	0.06	0.04
	CV% geometric mean	30.70	29.45
	Median	0.057	0.045
	Range	0.03–0.11	0.02–0.09

FCT = Film-coated tablet: single dose of 1080-mg deferasirox oral film-coated tablets (3 tablets × 360 mg)
DT = Dispersible tablet/reference: single dose of 1500-mg deferasirox dispersible tablets for oral suspension (3 tablets × 500 mg)
Source: Table 14.2-2.3

The following table presents the summary results of the statistical analysis for the bioequivalence metrics, $AUC_{0\text{-last}}$, AUC_{inf} and C_{max}.

Table 11-3 Treatment comparison of primary pharmacokinetic results: geometric mean ratio and 90% CI (PAS)

PK variable (unit)	Treatment	N	Adjusted geometric mean	Geometric mean ratio (90% CI)*	
AUClast (µmol × h/L)	DT	32	1270.79		
	FCT	32	1273.78	1.00	(0.932–1.078)
AUCinf (µmol × h/L)	DT	32	1327.01		
	FCT	32	1307.04	0.98	(0.916–1.059)
Cmax (µmol/L)	DT	32	81.54		
	FCT	32	105.83	1.30	(1.203–1.400)

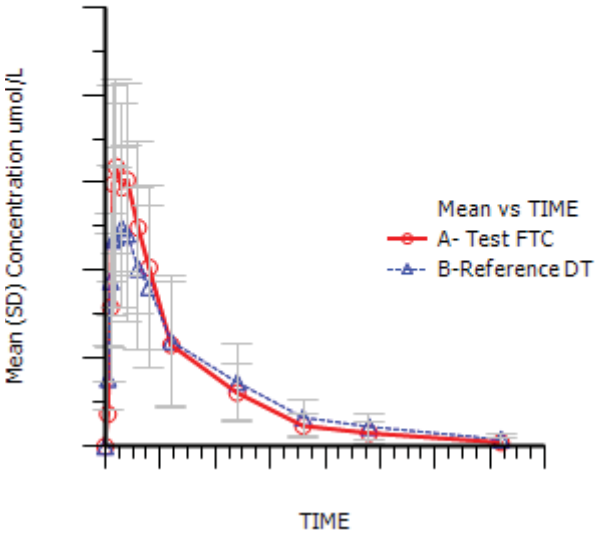
FCT = Film-coated tablet: single dose of 1080-mg deferasirox oral film-coated tablets (3 tablets × 360 mg)
DT = Dispersible tablet/reference: single dose of 1500-mg deferasirox dispersible tablets for oral suspension (3 tablets × 500 mg)
CI = confidence interval
* Comparisons were based on FCT vs. DT
Source: Table 14.2-1.1

The results indicate that $AUC_{0\text{-last}}$, AUC_{inf} are within the 80-125% criteria for bioequivalence, but C_{max} fails these criteria (90% CI 120-140%), indicating that the reference Exjade and the proposed Jadenu products are not bioequivalent.

Reviewer's Assessment of Pivotal BE Study F2102 :

This Reviewer confirmed the BE results provided by the Applicant. The Phoenix software (Phoenix 64 Build 6.3.0.395) was used to re-analyze the deferasirox plasma concentration. The following graph and table present the results that were obtained using Phoenix software.

The mean plasma deferasirox concentration-time profile after single dose 1080 mg (360 mg X 3) FTC vs single dose 1500 mg (500 mg X 3) DT



PK variable	Unit	Treatment	N	Geometric mean	Geometric mean ratio (% Ref)	90 % CI
Ln(Cmax)	umol/L	FTC (test)	32	105.83	1.30	120.28-140.05
		DP (ref)	32	81.54		
Ln(AUClast)	umol x h/L	FTC (test)	32	1273.44	1.00	93.17-107.77
		DP (ref)	32	1270.86		
Ln(AUCinf)	umol x h/L	FTC (test)	32	1306.69	0.98	91.57-105.87
		DP (ref)	32	1327.10		

This Reviewer calculated the 90% confidence intervals (CI) of AUC_{last}, and AUC_{inf} and the results indicate that these PK parameters are within the acceptable limits of 80-125%. However, the mean Cmax of the proposed product is increased by 30% as compared to that of the Exjade tablets and the 90% CI for Cmax is between 120.28-140.05%, which is outside of the acceptable bioequivalence limits of 80-125%.

2.3 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

In those cases that the 90% CI for geometric mean ratio of AUC_{last}, AUC_{inf} or C_{max} for the test and reference falls outside the BE boundaries, the clinical impact (i.e., safety and efficacy) of the failed PK parameters are evaluated and the decision to deviate or not from the FDA's acceptance criteria for BE and accept or reject a failed BE study, is primary based on the input from the Clinical and Clinical Pharmacology teams.

Therefore, in order to fully assess and understand the safety implication of a 30% higher Cmax, a brief background on the approved Exjade product is provided below.

- Exjade was approved on November 2, 2005, under the accelerated approval regulations. The approval letter included eleven post-marketing commitments, which required that the Applicant conduct additional adequate and well-controlled studies to verify and describe the clinical benefit. According to the Annual Status Report Review (dated 01/07/2015 and authored by Diane Leaman), at the present time still there are three delayed and six on going post-marketing requirements/commitments that have not been fulfilled.

- Briefly the scope of the pending PMC/PMRs are to conduct efficacy and safety studies in different patient populations (such as iron overloaded patients with non-transfusion dependent thalassemia, in patients with myelodysplastic syndromes and transfusional iron overload, pediatric patients with non-transfusion dependent iron overload), (b) (4) and an enhanced pharmacovigilance study for patients with MDS.

- According to the Exjade's label[2], there is a black box warning (added after NDA's approval) that Exjade may cause renal failure, hepatic failure and death in some patients and gastrointestinal hemorrhage which also may be fatal especially in elderly patients. In addition, Exjade has warnings and precautions for bone marrow suppression, toxicity due to decreased hepatic, renal and/or cardiac function in elderly population, serious and severe hypersensitivity reactions, and severe skin reaction listed in the label.

In order to evaluate the clinical impact of a 30% increase in Cmax, the Applicant provided an exposure-response analysis for safety using data from clinical trials with Exjade tablets. The Office of Clinical Pharmacology evaluated these PK/PD data. The OCP review indicates "that 30% increase in Cmax Jadenu Cmax is not clinically meaningful" and includes the following statements;

- Exposure-response analyses using tablets for oral suspension clinical trial data in patients showed that renal laboratory abnormalities are not strongly associated with the deferasirox Cmax.
- Only minor safety observations such as nausea and headaches were reported at Cmax in historical deferasirox tablets for oral suspension trials'

[2] http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3495a70c-870c-4968-940e-8baea152cf85

- Despite the 30% increase in mean Cmax with Jadenu compared to the tablet for oral suspension, the Cmax values with Jadenu were still within the overall range of those observed with the tablet for oral suspension formulation in healthy subjects and patients."

For specific details, refer to the OCP's review authored by Drs. W. Hsu, M. Lian, M. Nitin, and S. Schrieber dated 02/03/2014 in DARRTS.

Although, the Division of Biopharmaceutics agrees with OCP's PK/PD analysis that renal lab abnormalities are not associated with deferasirox Cmax, and the observed Cmax values with Jadenu were within the overall range of those observed with Exjade; there are remaining questions about the impact of deferasirox's higher Cmax on the overall safety of the product, as described in the black box associated with hepatic failures, gastrointestinal hemorrhages and the role of decreased cardiac function in elderly population. Therefore, it is the Division of Biopharmaceutics opinion that the benefits of Jadenu on overcoming the palpability issues associated with Exjade, do not outweigh the potential probability of an increased risk adverse events or safety issues associated with 30% increase in mean Cmax.

Therefore, the Division of Biopharmaceutics is deferring to the clinical division to make the decision about the clinical implications of the 30% increase in Cmax on the hepatic failures, gastrointestinal hemorrhages and toxicity seen in the elderly population.

2.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Refer to the Clinical Pharmacology Review.

2.5 Bioanalytical Method Validation Section

2.5.1 How the active moieties and/or metabolites are identified and measured in the plasma in the biopharmaceutics studies? What bioanalytical methods are used to assess concentrations?

The Bioanalytical method utilizes protein precipitation for deferasirox and the associated iron complex (Fe-(deferasirox)$_2$, AML644) in human plasma followed by analysis of the reconstituted samples by LC-MS/MS using Electro Spray Ionization. Benazepril HCl and warfarin were used as an internal standard for deferasirox and associated iron complex, respectively.

2.5.2 What is the range of the standard curve? How does it relate to the requirements for the clinical studies? What curve fitting techniques are used? What are the lower and upper limits of quantification

(LLOQ/ULOQ, and assay validation parameter: accuracy, precision, selectivity, sample stability, etc.?

The concentration range of standard curve had seven levels were between 0.670 µmol/L (LLOQ) to 26.8 µmol/L (ULOQ) for deferasirox, and were between 0.314 µmol/L (LLOQ) and 12.6 µmol/L (ULOQ) for AML644. The concentration vs response data is fit using linear regression analysis which described by the y=ax+b equation in which y is the peak ratio of analytes to the internal standard and x is the concentration of analytes in concentration standards.

For full details on the assessment of the bioanalytical method and its validation, please refer to the clinical pharmacology review for the Original NDA 21882 by S. Alfayoumi dated 10/1/2005 in DARRTS.

Reviewer's Assessment:
The Applicant provided acceptable information to support the validity of the bioanalytical method for determination of deferasirox in human plasma. The detailed information is included in the link below:
\\cdsesub1\evsprod\nda206910\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\icl670f2102\dmpk-rcicl670f2102--compliance-and-drug-concentration-data.pdf

2.6 Audit/Inspection reports of Study F2102 (clinical and bio-analytical sites)

It is noted that the clinical and bioanalytical site inspections were not performed for the bioequivalence study covered in this review based on a risk assessment of the studies' impact and prior inspections at the same or related sites by the Office of Scientific Investigations.

Clinical Site
The Office of Scientific Investigation (OSI) memorandum (Dr. Jyoti B. Patel, dated 10/22/2014) recommends the acceptance of the clinical data for the study F2102 in NDA 206910, without clinical site inspection.

Analytical Site
OSI recommends the acceptance of the analytical portion of study F2102 without the analytical site inspection.

3 GENERAL BIOPHARMACEUTICS (IN VITRO)

3.1 DISSOLUTION METHOD

3.1.1 What is the proposed dissolution method?

The dissolution method proposed as a quality control test for deferasirox film coated tablets is summarized below:

USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium
USP II	75 rpm	900 mL	37 ± 0.5°C	Phosphate Buffer pH 6.8 with 0.5% polysorbate 20

3.1.2 What data are provided to support the adequacy of the proposed dissolution method (e.g., medium, apparatus selection, rotation speed, etc.)?

The following data were collected during the development and validation of the dissolution method.

(b) (4)

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3.1.6 Is the proposed method acceptable? If not, what are the deficiencies?

As previously discussed, the dissolution data show very fast dissolution profile ((b) (4)% at (b) (4) minutes) for a low solubility drug such as deferasirox using the proposed dissolution method. The proposed dissolution method is not discriminating, but it is acceptable as a QC test.

4 DISSOLUTION ACCEPTANCE CRITERION

4.1 What is the proposed dissolution acceptance criterion for this product?

Proposed Dissolution Acceptance Criterion for Deferasirox Film Coated Tablets
Q= (b) (4)% at (b) (4) min

4.2 What data are available to support this criterion?

The Applicant did not provide complete dissolution profile information to support the proposed acceptance criterion. The dissolution data from stability batches (up to 12 month) for all strengths was collected only at the proposed (b) (4) minutes time point. These data show approximately 100 % drug release at (b) (4) minutes.

4.3 Is the acceptance criterion acceptable? If not, what is the recommended criterion? Is the setting of the dissolution acceptance criterion based on data from clinical and registration batches? If not, is the setting based on BE or IVIVC data?

The proposed acceptance criterion of Q = (b) (4)% in (b) (4) min is not acceptable. Based on the provided data a criterion of Q= (b) (4)% in 15 minutes is recommended.

5 DRUG PRODUCT FORMULATION DEVELOPMENT AND BRIDGING ACROSS PHASES

5.1 What are the highlights of the drug product formulation development?

The basis of the approval for the proposed drug product is the pivotal PK study F2102 comparing the film coated tablets to the approved Exjade tablets for oral suspension. (b) (4)

5.2 Are all the strengths evaluated in the pivotal clinical trials? What data are available to support the approval of lower strengths?

The Applicant conducted the pivotal PK study on the highest strength (360 mg), and requested a biowaiver for the lower strengths (90 mg and 180 mg). The evaluation of the pivotal BE study and the biowaiver request are discussed in the Sections 2 and 5 of this review, respectively.

5.3 Are there any manufacturing changes implemented (e.g. formulation changes, process changes, site change, etc.) to the clinical trial formulation? What information is available to support these changes?

Not Applicable

6 DISSOLUTION APPLICATIONS

6.1 BIOWAIVERS

6.1.1 Is there a request for a waiver of the submission of in vivo BE data (Biowaiver)? What is the purpose of the biowaiver request?

The Applicant submitted a biowaiver request for the lower strengths (90 mg and 180 mg). A biowaiver can be granted for the lower strengths provided 1) highest strength is BE to the listed drug 2) lower strengths are proportionally similar in composition to the highest strength, 3) similar dissolution profiles between lower strengths and higher strengths for which BE study is performed.

As discussed in Section 2 of this review, the highest strength was not found bioequivalent to the listed drug product, therefore the ***biowaiver request for lower strengths is not granted.***

Below are the additional information provided in support of the biowaiver request
Comparative dissolution profiles in three media 0.1 N HCl, pH 1.2 + 0.5% Tween 20, acetate buffer, pH 4.5 +0.5% Tween 20, and phosphate buffer, pH 6.8 +0.5% Tween 20).

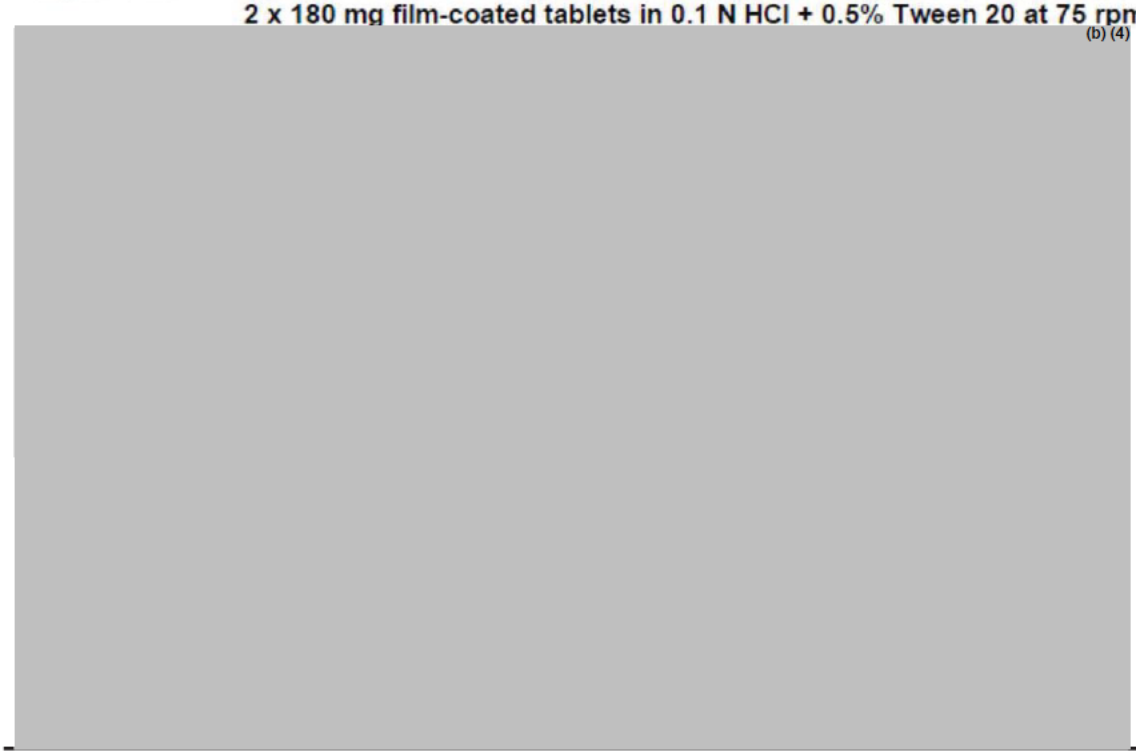
0.1 N HCl + 0.5% Tween 20 at 75 rpm

Table 3-12 Comparison of dissolution data of ICL670 360 mg, 4 x 90 mg and 2 x 180 mg film-coated tablets in 0.1 N HCl + 0.5% Tween 20 at 75 rpm

	(%) Percent dissolution in 0.1N HCl at 75 rpm		
Batch #	AEUS/2012-0106	H123JI	H134JI
Time (min)	1 x 360 mg	4 x 90 mg	2 x 180 mg
10	(b) (4)		
20			
30			
45			
60			

Reference: BVA140219_02, AVB140219_03, AVB140207_01

Figure 3-12 Comparison of dissolution data of ICL670 360 mg, 4 x 90 mg and 2 x 180 mg film-coated tablets in 0.1 N HCl + 0.5% Tween 20 at 75 rpm



Acetate Buffer pH 4.5 + 0.5% Tween 20 at 75 rpm

Table 3-11 **Comparison of dissolution data of ICL670 360 mg, 4 x 90 mg and 2 x 180 mg film-coated tablets in 4.5 Acetate buffer + 0.5% Tween 20 at 75 rpm**

	(%) Percent dissolution in 4.5 acetate at 75 rpm		
Batch #	AEUS/2012-0106	H123JI	H134JI
Time (min)	1 x 360 mg	4 x 90 mg	2 x 180 mg
10	(b) (4)		
20			
30			
45			
60			

Reference: AVB140219_04, BVA140219_03, DKR140211_02

Figure 3-11 **Comparison of dissolution data of ICL670 360 mg, 4 x 90 mg and 2 x 180 mg film-coated tablets in 4.5 Acetate buffer + 0.5% Tween 20 at 75 rpm**

Phosphate buffer pH 6.8 + 0.5% Tween 20 at 75 rpm

Table 3-10 Comparison of dissolution data of ICL670 360 mg, 4 x 90 mg and 2 x 180 mg film-coated tablets in 6.8 Phosphate buffer + 0.5% Tween 20 at 75 rpm

	(%) Percent dissolution in 6.8 Phosphate at 75 rpm		
Batch #	AEUS/2012-0106	H123JI	H134JI
Time (min)	1 x 360 mg	4 x 90 mg	2 x 180 mg
10			(b) (4)
20			
30			
45			
60			

Reference: AVB140206_01, BVA140205_03, BVA131211_02

Figure 3-10 Comparison of dissolution data of ICL670 360 mg, 4 x 90 mg and 2 x 180 mg film-coated tablets in 6.8 Phosphate buffer + 0.5% Tween 20 at 75 rpm

Reviewer's Comments:

Drug release in pH 1.2 and 4.5 reaches a plateau at around (b) (4) % and (b) (4) % respectively due to its low solubility in acidic media. In addition drug release profiles are overlapping in pH 6.8 with 0.5% surfactant for all strengths. Dissolution profiles indicate similarity between the higher and lower strengths. It should be noted that 4 90 mg and 2* 180 mg tablets were utilized for dissolution data comparisons. However, the dissolution method is not discriminating and therefore any dissolution differences among the strengths will not be detected.*

6.2 SURROGATES IN LIEU OF DISSOLUTION

6.2.1 Are there any manufacturing parameters (e.g. disintegration, drug substance particle size, etc.) being proposed as surrogates in lieu of dissolution testing? What data is available to support this claim?

No

6.3 DISSOLUTION AND QBD

6.3.1 If the application contains QbD elements, is dissolution identified as a CQA for defining design space?

The Applicant employed Quality by Design (QbD) and Quality Risk Management (QRM) principles in the manufacturing process development in line with ICHQ8, Q9, and Q10 guidances. The manufacturing process development plan follows classical QbD approach:

- Quality Target Product Profile
- Risk assessment
- Design of experiment (DoE)
- Design space
- Verification at full scale
- Continual verification

A statistical design of experiment (DoE) study was used to screen for the main effects using 7 factors (see above) at 2 levels, resulting in 16 experimental runs. The response variables of this experiment include:

(b) (4)

The Applicant's proposed control strategy and manufacturing settings for CPPs and non-CPPs were considered adequate.

For specific details on the Design Space refer to the Review Memo by Dr. Debasis Ghosh, Ph.D., dated Nov 20, 2014 in DARRTS.

6.3.2 Was dissolution included in the DoE? What raw materials and process variables are identified as having an impact on dissolution? What is the risk assessment been performed to evaluate the criticality of dissolution?

Particle size distribution of the (b) (4) and low and high harness of the core tablets were evaluated with dissolution. The percent of drug released at (b) (4) minute time point of variant tablets was similar.

6.3.3 What biopharmaceutics information is available to support the clinical relevance of the proposed design space?

No

6.3.4 Is there any dissolution model information submitted as part of QbD implementation? What is the regulatory application of the dissolution model in the submission? What data are provided to support the acceptability of the dissolution model?

No

7 EVALUATION OF RISK ASSESSMENT

The Table below presents the risk assessment for the dissolution quality attribute of the proposed deferasirox tablets.

Initial Quality Assessment			Final Review Assessment		
Product attribute / CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation Approach	Risk Evaluation [Acceptable/ Unacceptable]	Lifecycle Considerations/ Comments
Dissolution	Dissolution testing conditions and amount of surfactant in the formulation	Medium	Implementation of tighter dissolution acceptance criterion	Acceptable	The NDA's dissolution method was found acceptable. The amount of surfactant and disintegrant in the formulation impact the dissolution profiles.

* Risk ranking applies to product attribute/CQA (L, M, H)

8 LABELING

The biopharmaceutics labeling information is addressed by the assigned Clinical Pharmacology Reviewer.

9 BIOPHARMACEUTICS INFORMATION REQUESTS

The following Biopharmaceutics information request was issued;

The dissolution data from the Pivotal BE batch do not support your proposed dissolution acceptance criterion of Q= (b) (4) *% at* (b) (4) *minutes for Jadenu (deferasirox) tablets and is not acceptable. Based on the provided data, we recommend that you implement a dissolution acceptance criterion of Q=* (b) (4) *% at 15 minutes for Jadenu (deferasirox) tablets. Be aware that the setting of the dissolution acceptance criterion should be based on mean values and therefore, it must be recognized that some batches may require Stage 2 and, occasionally, Stage 3 testing.*

OFFICE OF CLINICAL PHARMACOLOGY (OCP) REVIEW

NDA:	206910, SDN 1
Submission Date:	May 30, 2014
Brand Name:	Jadenu
Generic Name:	Deferasirox
OCP Reviewer:	Vicky Hsu, Ph.D.
OCP Team Leader:	Sarah J. Schrieber, Pharm.D.
Pharmacometrics Reviewer:	Lian Ma, Ph.D.
Pharmacometrics Team Leader:	Nitin Mehrotra, Ph.D.
OCP Division:	Division of Clinical Pharmacology V
ORM division:	Division of Hematology Products
Sponsor:	Novartis
Submission Type, code:	505(b)(1), standard review
Formulation: strength(s)	Tablets (film-coated): 90, 180, 360 mg
Dosing Regimen:	In patients with transfusional iron overload: recommended initial dose is 14 mg/kg once daily. In patients with non-transfusion-dependent thalassemia (NTDT): recommended initial dose is 7 mg/kg once daily.
Indication(s):	1) Treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. 2) Treatment of chronic iron overload in patients 10 years of age and older with 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.

Table of Contents

1 EXECUTIVE SUMMARY

Deferasirox is an iron chelator. Jadenu is a film-coated tablet (FCT) formulation of deferasirox. Jadenu FCTs are a strength-adjusted formulation of deferasirox with higher bioavailability compared to Exjade, the tablets for oral suspension formulation which is an FDA-approved product for the treatment of patients with chronic iron overload (NDA 21882). The sponsor developed the Jadenu FCT formulation to address palatability issues associated with Exjade.

A PK comparability study evaluated deferasirox FCT vs. the tablet for oral suspension formulation. Biowaiver requests for the lower FCT strengths of 90 and 180 mg were submitted and PK/PD analyses for the highest proposed FCT strength of 360 mg were conducted. The comparability study and biowaiver requests were reviewed by ONDQA.

The bioavailability of FCT formulation was 36% greater than with tablets for oral suspension. In the PK comparability study, after strength-adjustment, the FCT formulation (i.e., 360 mg strength) was equivalent to tablets for oral suspension (i.e., 500 mg strength) with respect to the mean AUC under fasting conditions, however the mean C_{max} was increased by 30%. It is worth noting that the C_{max} values with FCT formulation are within range of those observed with the tablet for oral suspension formulation in healthy volunteers and patients. Furthermore, exposure-response analysis for safety was conducted by the sponsor using data from clinical trials with the deferasirox tablets for oral suspension formulation to evaluate the effect of a 30% increase in C_{max}. Based on the results from exposure-response analysis, the moderately higher C_{max} values observed with the new FCT formulation are not expected to be clinically meaningful.

A food-effect study involving administration of Jadenu to healthy subjects under fasting conditions and with a low-fat (fat content <7% of total calories) or high-fat (fat content >50% of total calories) meal indicated that the AUC and C_{max} were slightly decreased after a low-fat meal (by 11% and 16%, respectively). After a high-fat meal, AUC and C_{max} were increased by 18% and 29%, respectively. The increases in C_{max} due to the change in formulation and due to the effect of a high-fat meal may be additive. Therefore, it is recommended that Jadenu should be taken on an empty stomach or with a low-fat meal.

1.1 Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology V and Division of Pharmacometrics, has determined that there is sufficient clinical pharmacology information provided in this NDA to support an approval recommendation.

1.2 Post Marketing Requirements/Commitments

None.

1.3 Signatures

Vicky Hsu, Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology V

Lian Ma, Ph.D.
Pharmacometrics Reviewer
Division of Pharmacometrics

Sarah J. Schrieber, Pharm.D.
Clinical Pharmacology Team Leader
Division of Clinical Pharmacology V

Nitin Mehrotra, Ph.D.
Pharmacometrics Team Leader
Division of Pharmacometrics

1.4 Clinical Pharmacology Summary

Deferasirox is an iron chelator. Jadenu is a film-coated tablet (FCT) formulation of deferasirox. Jadenu FCTs are a strength-adjusted formulation of deferasirox with higher bioavailability compared to Exjade, the tablets for oral suspension formulation which is an FDA-approved product for the treatment of patients with chronic iron overload (NDA 21882). The sponsor developed the FCT formulation to address palatability issues associated with Exjade.

A PK comparability study evaluated deferasirox FCT vs. the tablet for oral suspension formulation. Biowaiver requests for the lower FCT strengths of 90 and 180 mg were submitted and PK/PD analyses for the highest proposed FCT strength of 360 mg were conducted. The comparability study and biowaiver requests were reviewed by ONDQA.

The bioavailability (based on AUC) of Jadenu was 36% greater than with deferasirox tablets for oral suspension. After strength-adjustment, Jadenu (i.e., 360 mg strength) was equivalent to deferasirox tablets for oral suspension (i.e., 500 mg strength) with respect to the mean AUC under fasting conditions, however the mean C_{max} was increased by 30% (90% CI: 1.2, 1.4).

The exposure-response analysis for safety using data from clinical trials with deferasirox tablets for oral suspension indicated that 30% increase in Jadenu C_{max} is not clinically meaningful;

- Exposure-response analyses using tablets for oral suspension clinical trial data in patients showed that renal laboratory abnormalities are not strongly associated with the deferasirox C_{max}..
- Only minor safety observations such as nausea and headaches were reported at C_{max} in historical deferasirox tablets for oral suspension trials.
- Despite the 30% increase in mean C_{max} with Jadenu compared to the tablet for oral suspension, the C_{max} values with Jadenu were still within the overall range of those observed with the tablet for oral suspension formulation in healthy subjects and patients.

A food-effect study involving administration of Jadenu to healthy subjects under fasting conditions and with a low-fat (fat content <7% of total calories) or high-fat (fat content >50% of total calories) meal indicated that the AUC and C_{max} were slightly decreased after a low-fat meal (by 11% and 16%, respectively). After a high-fat meal, AUC and C_{max} were increased by 18% and 29%, respectively. The increases in C_{max} due to the change in formulation and due to the effect of a high-fat meal may be additive. Therefore, it is recommended that Jadenu should be taken on an empty stomach or with a low-fat meal.

2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the proposed dosage(s) and route(s) of administration?

The applicant proposes a Jadenu dosing regimen of 14 mg/kg orally once daily in patients with transfusional iron overload and 7 mg/kg orally once daily in patients with non-transfusion-dependent thalassemia (NTDT) syndromes.

2.2 General Clinical Pharmacology

In addition to the information included in this review, also refer to the FDA-approved product labeling for Exjade and the clinical pharmacology review of original NDA 21882 (deferasirox tablets for oral suspension) (review dated 10/1/2005 authored by S. Alfayoumi).

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

A summary of completed deferasirox clinical studies to support the NDA is shown in **Table 1**.

- Three single dose clinical pharmacology studies with the FCT (the relative bioavailablity study F2101, the pivotal PK comparability study F2102, and the food effect study F2103).
- (b) (4)
- A PK/PD analysis of a large clinical study in the target population (study A2409) of the tablets for oral suspension formulation to determine the relative contributions of AUC and C_{max} to the safety and efficacy profiles of deferasirox.

The clinical pharmacology studies were single-center phase 1 studies and were conducted in healthy volunteers in the US.

Table 1. Overview of clinical pharmacology studies and additional analyses to support the FCT application

Study	Short Title	Design Sample size (n)	Dose Formulation	Study population
F2101	Pilot relative bioavailability study; comparing three new formulations vs. reference	Randomized, open-label, single-center, four-period cross-over (20)	500 mg tablet for oral suspension	Healthy subjects
F2102	PK comparability of FCT vs. reference	Randomized, open-label, single-center, two-period cross-over (32)	1080 mg FCT, 1500 mg tablet for oral suspension	Healthy subjects

F2103	Food effect of the FCT	Randomized, open-label, single-center, three-period cross-over (25)	1080 mg FCT	Healthy subjects
				(b) (4)
A2409	Efficacy, and safety of the tablet for oral suspension	One-year, open-label, single arm, multi-center	10-30 mg/kg tablet for oral suspension	Patients

2.2.2 Exposure-Response

2.2.2.1 Does the exposure-response (E-R) relationship for safety support the proposed dosing of the film-coated tablets (FCT)?

Yes, exposure-response analyses for safety conducted by the sponsor support the proposed dosing of the FCT.

After strength-adjustment, Jadenu (i.e., 360 mg strength) was equivalent to deferasirox tablets for oral suspension (i.e., 500 mg strength) with respect to the mean AUC under fasting conditions, however the mean C_{max} was increased by 30% (**Table 2**). Refer to the ONDQA review by B. Zolnik for more details.

The results of exposure-response analyses indicate that safety of deferasirox is largely driven by overall exposure (AUC), and changes in C_{max} by a magnitude of ~30% are unlikely to result in worsening renal laboratory values. Furthermore, no major safety findings were reported with the tablet for oral suspension formulation. The C_{max} values of the FCT formulation are within the range of C_{max} values observed with the tablet for oral suspension formulation in both healthy subjects and patients.

As shown in **Table 2**, the PK comparability study F2102 demonstrated equivalent AUC between the FCT and the tablet for oral suspension by meeting the standard bioequivalent criteria (0.80-1.25), whereas the mean C_{max} of the FCT was 30% higher than the tablet for oral suspension.

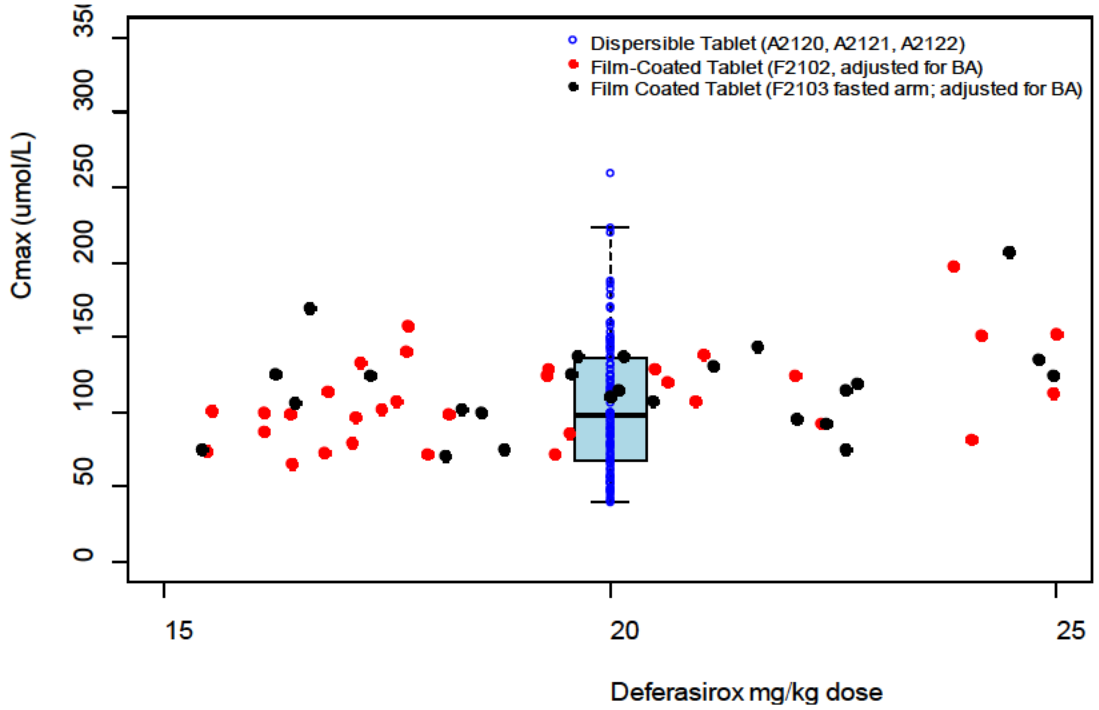
Table 2. Study F2102 PK comparability results. FCT1080 mg FCT (28% dose adjustment from the tablets for oral suspension) vs. 1500 mg tablets for oral suspension (data reviewed by ONDQA).

PK Parameter	Ratio	90% CI	
		Lower	Upper
C_{max}	**1.298**	**1.203**	**1.401**
AUC_{last}	1.002	0.932	1.078
AUC_{inf}	0.985	0.916	1.059

Ratio: FCT/tablet for oral suspension

Although C_{max} did not meet the bioequivalent criteria, individual C_{max} values of FCT were within the range of historical C_{max} values observed with the tablets for oral suspension formulation in healthy subjects. **Figure 1** includes C_{max} data from healthy subjects receiving a) 20 mg/kg deferasirox tablets for oral suspension in previous clinical pharmacology studies, b) FCT in study F2102, and c) FCT under fasted conditions in study F2103. Extensive clinical safety data with the range of observed C_{max} values with the tablet for oral suspension formulation revealed no effect on QT interval and only minor safety findings such as nausea and headaches at C_{max}.

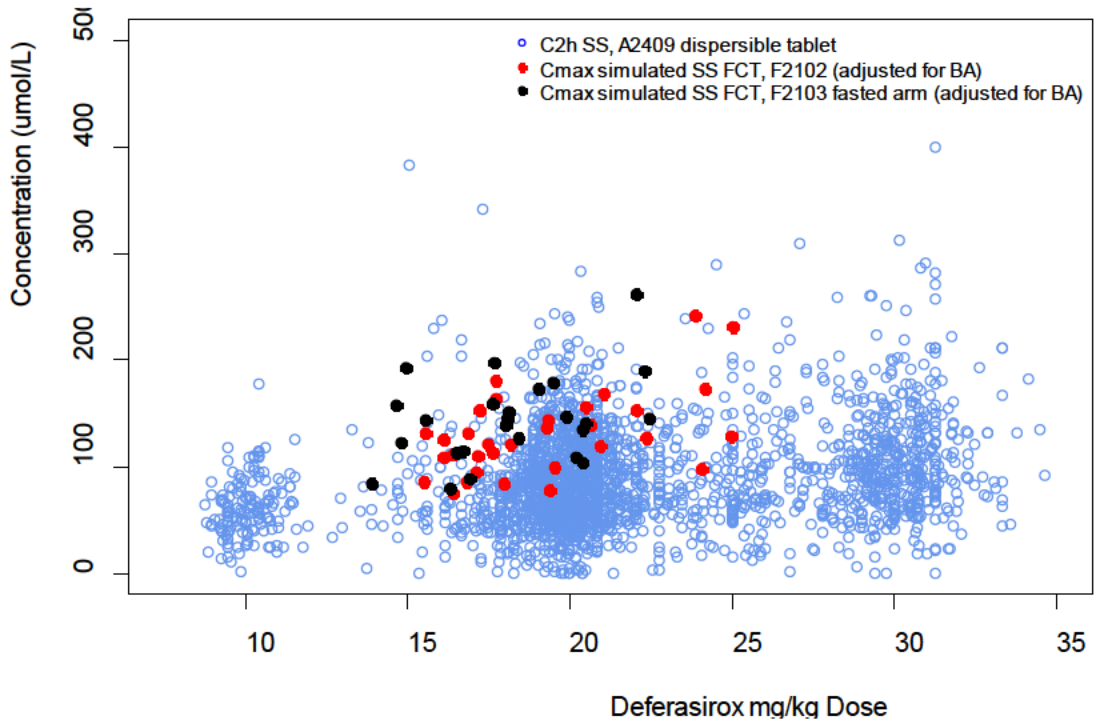
Figure 1. Deferasirox C_{max} comparison: Historical healthy subject tablets for oral suspension (20 mg/kg) data with and FCT data from studies F2102 and F2103 at various mg/kg doses.



(Source: Sponsor's Summary of biopharmaceutic studies. Figure 5-1.)

Furthermore, in a large multicenter study A2409 in patients diagnosed with transfusion-dependent iron overload, deferasirox PK data were collected in a sub-group of patients (n=1112) at pre-dose (C_{trough} (i.e., measure of AUC) and 2 hours post-dose (C_{2h} (i.e., measure of C_{max}) on Day 1 of Weeks 12 and 28, and at end of study. As shown in **Figure 2**, the steady-state C_{max} values for the FCT were estimated by a nonparametric superposition approach (based on linear elimination kinetics in studies F2102 and study F2103), and were within the range of observed steady-state C_{2h} values with the tablet for oral suspension formulation. Of note, deferasirox exposure in iron-overloaded patients, based on C_{max} and AUC values, is found to be 34-57% lower in patients (study A0105F) than those in healthy volunteers (study A2120, A2121, A2122).

Figure 2. Observed steady-state C_{2h} for tablets for oral suspension in patients (Study A2409) vs. simulated steady-state C_{max} for FCT (Studies F2102 and F2103).



FCT: full-coated tablets; SS: steady state; BA: bioavailability. *(Source: Sponsor's Summary of biopharmaceutic studies. Figure 5-2.)*

To determine if the increased C_{max} observed with the FCT is expected to have a clinically meaningful impact on safety, exposure-response analyses were performed by the sponsor based on tablet for oral suspension data from study A2409. Renal laboratory values were chosen as the safety signals of interest; these variables have known effects on deferasirox exposure. C_{max} (C_{2h}) and AUC (C_{trough} as surrogate) were assessed as exposure measures. Various approaches were explored in the analyses, including linear regression, logistic regression, linear mixed-effect and proportional odds model, using univariate and multivariate methods. Please refer to **Appendix 4.1** *Sponsor's PK/PD analysis* for more details.

The results from the exposure-response analyses generally showed that renal laboratory value abnormalities are more strongly associated with AUC than C_{max}. Even for the worst-case scenario, an overall 70% increase in C_{max} (FCT with a high fat meal compared to the tablet for oral suspension under fasting condition) is unlikely to cause clinically significant increases in serum creatinine.

2.5 General Biopharmaceutics

2.5.1 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Study CICL670F2103 was a single-center, open-label, randomized, three-period, six-sequence, cross-over study to evaluate the effect of food on the pharmacokinetics of deferasirox film-coated tablets (FCT) in healthy subjects. The three periods tested the effect of the following dosing treatments:

- **Treatment A (fasted)**: 1080 mg deferasirox FCT was administered to subjects after overnight fasting for at least 10 hours.
- **Treatment B (low-fat meal)**: 1080 mg deferasirox FCT was administered to subjects within 30 minutes after the start of a low-fat breakfast (6.2% fat content). The entire low-fat breakfast was consumed by the subject prior to dosing.
- **Treatment C (high-fat meal)**: 1080 mg deferasirox FCT was administered to subjects within 30 minutes after the start of a high-fat breakfast (58.6% fat content). The entire high-fat breakfast was consumed by the subject prior to dosing.

A total of 28 subjects were randomized and of these, 24 subjects completed study treatments. PK samples were collected up to 72 hours post-dose with an 8-day washout period between treatments.

The effect of food on deferasirox FCT PK is shown in **Table 3.** The results showed that deferasirox FCT PK after a low-fat meal was generally comparable to deferasirox FCT PK under fasted condition—C_{max} and AUC decreased approximately 16% and 11%, respectively, when compared to fasted condition. In contrast, a high-fat meal increased deferasirox FCT C_{max} and AUC by approximately 29% and 18%, respectively, when compared to fasted condition.

Table 3 . Statistical analysis summary of primary PK parameters for deferasirox FCT.

					Treatment comparison 90% CI		
PK parameter (unit)	Treatment	n*	Adjusted geometric mean	Comparison (s)	Geometric mean ratio	Lower	Upper
AUCinf (µmol/L*hr)	A	25	1570	-	-	-	-
	B	22	1390	B/A	0.890	0.835	0.948
	C	25	1840	C/A	1.18	1.11	1.25
AUClast (µmol/L*hr)	A	25	1520	-	-	-	-
	B	24	1340	B/A	0.886	0.835	0.940
	C	25	1780	C/A	1.17	1.11	1.24
Cmax (µmol/L)	A	25	113	-	-	-	-
	B	24	94.1	B/A	0.835	0.774	0.901
	C	25	145	C/A	1.29	1.20	1.39

Model is a linear mixed model of the log transformed PK parameters with sequence, period and treatment as fixed effects, and subject nested within sequence as random effect. Results were back transformed to get adjusted geo-mean, GM ratio, and 90% CI.

n* = number of subjects with non-missing PK parameter for the corresponding treatment period.

Treatment A or reference: Single dose of 1080 mg deferasirox (3 x 360 mg film-coated tablets) under fasted conditions (with water).

Treatment B: Single dose of 1080 mg deferasirox (3 x 360 mg film-coated tablets) with a low-fat breakfast.

Treatment C: Single dose of 1080 mg deferasirox (3 x 360 mg film-coated tablets) with a high-fat breakfast.

In regards to safety, this single-dose food effect study in healthy subjects was well tolerated under both fasted and fed conditions, and no new safety signals were observed.

The deferasirox C_{max} increases as a result of the formulation change and the effect of a high-fat meal may be additive. Therefore, deferasirox FCT is recommended to be taken on an empty stomach or with a low-fast meal.

2.6 Analytical Section

Deferasirox pharmacokinetic drug concentrations were determined using a validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) method. The assay range was 0.670 to 53.6 µmol/L. For full method details, refer to the clinical pharmacology review of original NDA 21882 (deferasirox tablets for oral suspension) (review dated 10/1/2005 authored by S. Alfayoumi).

3 LABELING RECOMMENDATIONS

The following sections were updated to include the food effect study results and instructions regarding food intake:

- DOSAGE AND ADMINISTRATION
- 2.3 Administration
- 12.3 Pharmacokinetics
- 17 PATIENT COUNSELING INFORMATION

4 APPENDICES

4.1 Sponsor's PK/PD analysis

Study A2409 was designed to provide efficacy and safety data over 52 weeks of treatment with deferasirox in patients presenting with evidence of transfusion-induced iron overload. The target patient pool consisted of patients with a serum ferritin level of ≥ 1000 ng/mL or patients presenting with a serum ferritin level <1000 ng/mL but with history of multiple transfusions (>20 transfusions or 100 mL/kg of packed red blood cells) and LIC >2 mg Fe/g dry weight. The initial recommended daily dose of deferasirox DT was 20 mg/kg/day body weight for patients, who had received blood transfusions with a frequency of about 2 to 4 units/month of packed red blood cells. An initial daily dose of 10 mg/kg/day or 30 mg/kg/day was permitted for patients receiving less or more frequent blood transfusions, respectively.

A total of 1,744 patients were enrolled into the study. Of these, 1112 contributed pharmacokinetic data. Average daily dose for all patients was 22.22 mg/kg (SD: 5.921), with the majority of these patients having no dose interruptions (77.6%), or only one dose interruption (15.1%). The PK endpoints in the A2409 PK/PD analyses were C2h on Day 1 after a single deferasirox dose, and the steady state PK parameters Ctrough,ss and C2h,ss, collected on both Week 12 and Week 28. The efficacy endpoint was serum ferritin at Week 12 and Week 28 and the safety endpoints were serum creatinine and creatinine clearance, collected at baseline, Week 4 (serum creatinine only), Week 12 and Week 28. Pre-dose or trough concentrations at steady state (Ctrough at Week 12 and Week 28) were used as a surrogate for AUC, and concentrations collected at 2 hours post-dose (C2h at Week 12 and Week 28) were used as surrogate for Cmax.

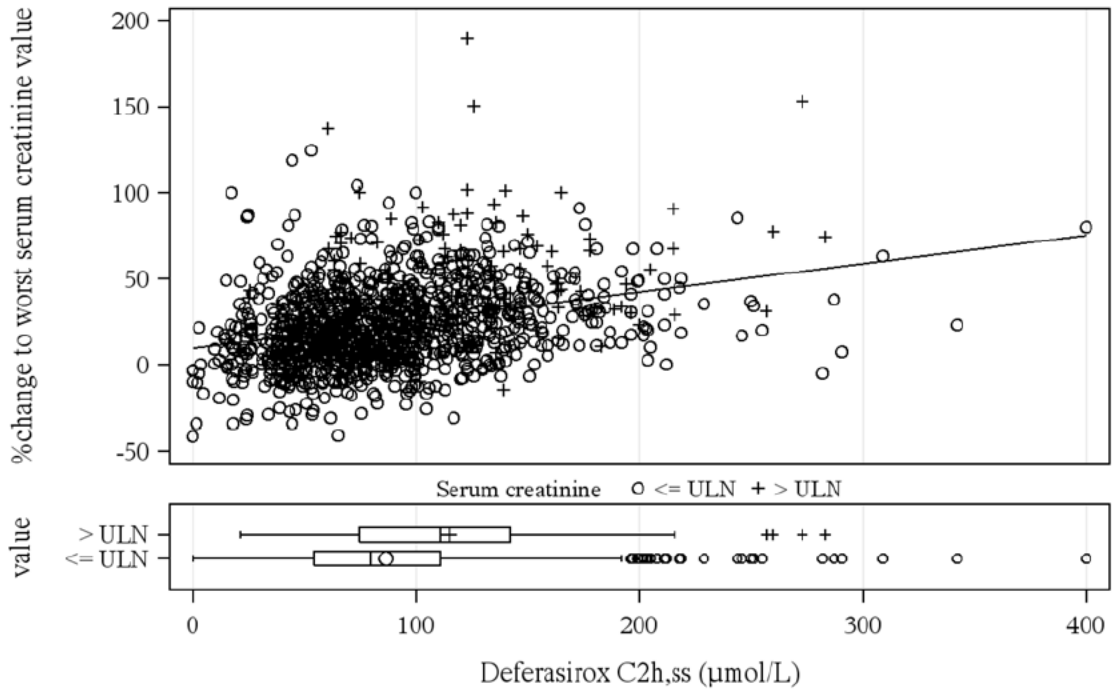
PK/PD analysis was performed by the sponsor on data from study A2409, to evaluate the relationship between pharmacokinetic parameters (C2h as a surrogate for Cmax, and Ctrough as a surrogate for AUC) and renal laboratory values (serum creatinine and creatinine clearance).

Effect of C2h,ss or Ctrough,ss on percentage change from baseline in serum creatinine

Scatterplots of the percent changes in serum creatinine versus C2h,ss or Ctrough,ss were generated to further explore the relationship between renal function and PK parameters. For this analysis notable serum creatinine values were defined as: (1) increase in serum creatinine from baseline >33% at 2 consecutive measurements at least 7 days apart (FLAG 1) and (2) increase in serum creatinine >33% from baseline and value >ULN at 2 consecutive measurements at least 7 days apart (FLAG 2). Notable values (FLAG1 or FLAG2) are displayed as (+) in the figures while all other values are depicted as (o) in **Figure 3** and **Figure 4**. **Figure 3** shows a weak positive correlation between the percent changes in serum creatinine and C2h,ss values at Week 12 and Week 28 (adj R-sq = 0.073). Although the median C2h,ss values for patients with notable serum creatinine

values are higher than those without, the distribution of C2h,ss among the two groups are largely overlapping.

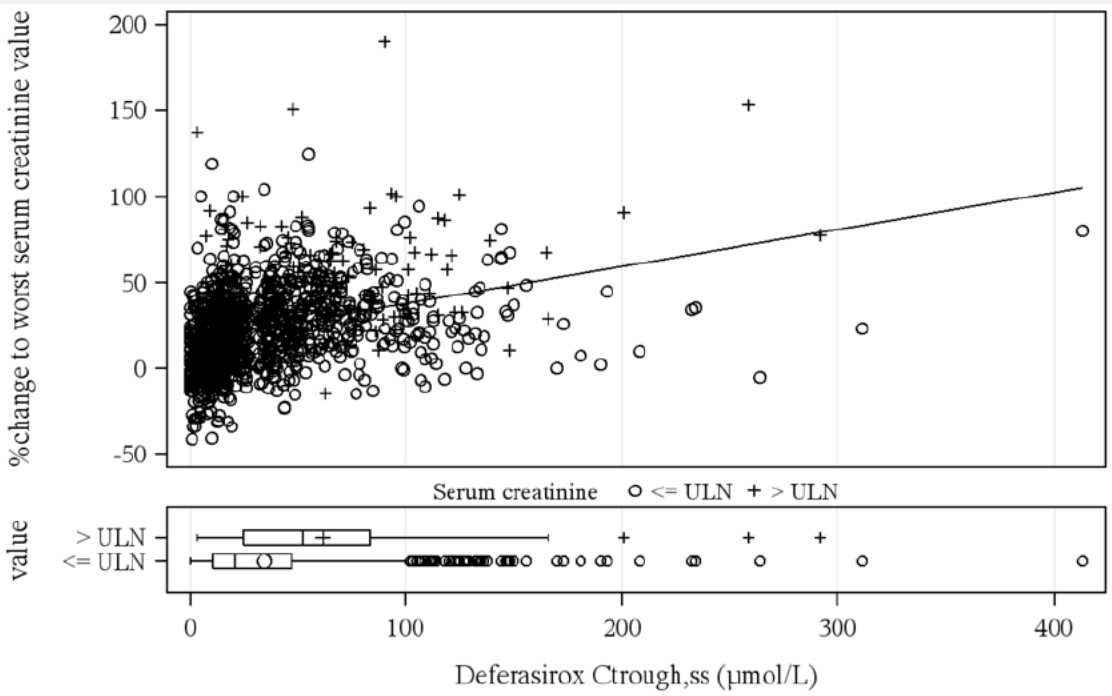
Figure 3. Percentage change from baseline in serum creatinine Week 12 and 28; Flag 2 criterion versus deferasirox C2h,ss



Results of Linear Regression: N = 927 (N = 67 with Flag2 = H and N = 860 with Flag2 = N)
Intercept = 7.987, Slope [90%CI] = 0.144 [0.117,0.172], Adj R-Sq = 0.073
FLAG 2: =>33% increase in serum creatinine from baseline and >ULN at 2 consecutive measurements at least 7 days apart.

When analyzing the relationship between Ctrough,ss and percent changes in serum creatinine at Week 12 and Week 28, there is also a weak positive correlation (adj R-sq = 0.117), similar to results observed with C2h, although results show a slightly higher R-sq value with Ctrough,ss compared to C2h,ss (**Figure 4**). Similar to C2h,ss, median Ctrough,ss values for patients with notable serum creatinine values are higher than those without, and there is overlapping distribution of Ctrough,ss among the two groups. Moreover, notable serum creatinine values (FLAG2) are also randomly distributed over the range of Ctrough,ss values, similarly to C2h,ss. Moreover, similar relationship was observed for both PK parameters at Week 28. Finally, overall similar finding was seen when repeating the analyses with FLAG 1 notable values at Week 12 and Week 28.

Figure 4. Percentage change from baseline in serum creatinine Week 12 and 28; Flag 2 criterion versus deferasirox C2h,ss



Results of Linear Regression: N = 934 (N = 68 with Flag2 = H and N = 866 with Flag2 = N)
Intercept = 12.624, Slope [90%CI] = 0.230 [0.196,0.265], Adj R-Sq = 0.117
FLAG 2: =>33% increase in serum creatinine from baseline and >ULN at 2 consecutive measurements at least 7 days apart.

A linear mixed effect model analysis of log-transformed serum creatinine values was performed using log-transformed Ctrough,ss, log-transformed C2h,ss, and log-transformed baseline serum creatinine as fixed effects and patient as a random effect at Week 12 and Week 28 (**Table 3**). The analysis showed that for a 70% increase in Cmax (the increase observed with FCT when taken with a high-fat meal as compared to DT taken under fasted conditions), the ratio of serum creatinine values would increase by a ratio of 1.0176 (=1.70.03287) with upper bound of the 95% CI of 1.0245 (with all other factors held constant). This result can be re-stated as follows: two C2h values with ratio equal to 1.7 (i.e. 70% increase from one to the other) would result in two serum creatinine values whose ratio is 1.0176 (indicating a clinically insignificant increase of 1.76% in serum creatinine) when all other factors are held constant. The potential of multi-colinearity for log(C2h) and log(Ctrough) was assessed in the statistical model described above and did not show any multi-colinearity issue (Variance Inflation Factor (VIF)=1.56 and condition index <30).

Table 3. Linear mixed effect model of percent change in serum creatinine at Week 12 and Week 28

Parameter	Estimate	Standard error	T value	Pr >|t|	Lower	Upper
Log(baseline creatinine)	0.9593	0.01226	78.22	<0.0001	0.9391	0.9795
Log(C2h)	0.03287	0.007786	4.22	<0.0001	0.02005	0.04569
Log(Ctrough)	0.06504	0.004803	13.54	<0.0001	0.05713	0.07295

Pr: probability; T: T-test value

Effect of C2h,ss and Ctrough,ss on percentage change from baseline in creatinine clearance

A proportional odds model was performed to further elucidate the impact of each logtransformed PK parameter on renal function as represented by creatinine clearance, based on Week 12 data, Week 28 data and respectively pooled data from Week 12 and Week 28 (Table 4). The dependent variable in this analysis is categorical creatinine clearance with ordered clinically relevant categories of 90 ml/min or more, 60 to <90 mL/min, 40 to <60 mL/min, and <40 mL/min. The analysis based on Week 12 and Week 28 data showed that Ctrough,ss had a stronger impact on creatinine clearance change in categories ($p < 0.0001$) but C2h,ss had minimal impact ($p=0.2544$) after adjusting for Ctrough,ss. Furthermore, a C2h,ss increase by 1.7-fold would provide an odds ratio of worsening from baseline in creatinine clearance categories of 1.146 (0.906, 1.449). This further illustrates the lack of impact of C2h,ss on change in creatinine clearance categories, when adjusting for Ctrough,ss and indicates that the new formulations (comparable AUC but higher Cmax than the current formulation) would result in a comparable effect on renal function. Similar results were consistently observed for the Week 12 analysis (PT-Table 1-10a) and the Week 28 analysis (PT-Table 1-10b). The potential for multi-colinearity for log(C2h,ss) and log(Ctrough,ss) was assessed in the 3 statistical models described above and did not show any multi-colinearity issue (Variance Inflation Factor (VIF)<1.7 and condition index <30).

Table 4. Analysis of creatinine clearance categories versus steady state PK parameters - Week 12 and Week 28

Parameter	Estimate	Standard error	Pr > |t|	OR for a 70% increase in PK parameter (95% CI)
Log(baseline creatinine clearance)	-10.796	0.626	<0.0001	
Log(Ctrough)	0.975	0.141	<0.0001	1.678 (1.449, 1.942)
Log(C2h)	0.257	0.225	0.2544	1.146 (0.906, 1.449)

Pr: probability; T: T-test value

Sponsor's conclusion: The results demonstrate that Cmax after first dose did not predict the renal laboratory changes at Week 4. The ordinal logistic regression model showed that AUC (as estimated by Ctrough,ss) had a statistically significant impact on change in

creatinine clearance category (e.g. less than 60 ml/min to greater than or equal to 60 ml/min), but Cmax (as estimated by C2h,ss) did not. Furthermore, modeling suggests that a 70% increase in Cmax (the increase observed when the FCT was administered with a high fat meal) will not result in a clinically meaningful change in creatinine clearance category. The linear mixed effect model suggest that for a given Ctrough,ss value, a 70% increase in Cmax (the highest increase in Cmax observed across the clinical pharmacology studies of the new formulation), would result in a clinically insignificant increase in serum creatinine. When notable increases in serum creatinine (FLAG1 and FLAG2) were present, they were observed across all deferasirox Cmax, not just near the upper range of Cmax. Notable values – those with the greatest increase in serum creatinine tended to be clustered towards the lower end of the Cmax spectrum. Thus, clinically relevant increases in serum creatinine are not likely due to higher Cmax. In conclusion, based on these results, higher Cmax in a patient with same or similar AUC is not expected to result in clinically significant changes in renal function. Patient exposure to a deferasirox formulation that results in a higher Cmax than that observed with the dispersible tablet is not expected to increase the risk of safety findings.