CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216157Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 216157

Review # 1

Drug Name/Dosage Form	Voxelotor tablet for oral suspension
Strength	300 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Global Blood Therapeutics

SUBMISSIONS REVIEWED	DOCUMENT DATE
Original	6/25/21
Quality Amendment	7/21/21, 7/30/21, 10/08/21, 10/28/21

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Zhengfu Wang	Suong Tran
Drug Product	Dhanalakshmi Kasi	Mohan Sapru
Process/ Facility	Binjie Liang	Feiyan Jing
Biopharmaceutics	Jing Li	Poonam Delvadia
Regulatory Business Process Manager	Grafton Adams	
Application Technical Lead	Dhanalakshmi Kasi	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. **DMFs: None**

B. Other Documents: NDA 213137

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

From the Chemistry, Manufacturing and Controls (CMC)/quality perspective, NDA 216157 is recommended for approval. As part of this action, an expiration period of 36 months is granted for the 300 mg product stored at [redacted] 20°C to [redacted]°C (68°F to [redacted]°F).

II. Summary of Quality Assessments

A. Product Overview

Voxelotor is a small-molecule sickle hemoglobin polymerization inhibitor from Global Blood Therapeutics, Inc. developed for the treatment of sickle cell disease. Applicant referenced NDA 213137, Oxbryta® (voxelotor) tablets, 500 mg, which was approved on November 25, 2019 for the treatment of sickle cell disease in adults and pediatric patients 12 years of age and older. The drug product OXBRYTA® (voxelotor) tablets, for oral use, 300 mg is a new dosage form, which received breakthrough therapy, rare pediatric disease, orphan drug and fast track designations. The drug product formulation is as an immediate release solid oral dosage form with a high drug content. The tablets are intended to be dispersed in water or clear liquid vehicle before administration, giving a dispersion suitable for administration to pediatric population.

NDA 213137 is referenced for all CMC information related to the drug substance voxelotor and found adequate to support NDA 216157. The drug product manufacturing process involves [redacted]. Drug substance and drug product manufacturing, testing, and packaging facilities are adequate as per the facility review. The drug substance facility, [redacted] was withdrawn from the application as it was not used to manufacture the registration batches and development batches of drug substance. The proposed dissolution acceptance criterion (NLT [redacted]%(Q) in 15 min is deemed acceptable.

B. Quality Assessment Overview

Drug Substance

Voxelotor drug substance is a non-hygroscopic small synthetic molecule and does not contain any chiral center. It is a white to yellow to beige solid in crystalline Form II and has low aqueous solubility and its solubility in aqueous media at various pH ranges from slightly soluble to insoluble. Polymorphic form and particle size of the drug substance are routinely tested per release specification of the drug substance. The drug substance is placed in a (b) (4) . The retest period is (b) (4) months when stored at (b) (4) in the proposed container closure system.

Drug Product

OXBRYTA® (voxelotor) tablets, for oral use, 300 mg is an immediate release solid oral dosage form with a high drug content. The tablets are intended to be dispersed in water or clear liquid vehicle before administration, giving a dispersion suitable for administration to pediatric population. In-use stability data showed that the drug product is stable in water and other vehicles such as (b) (4), and Sprite soft drink at room temperature for 4 h. The excipients used in the drug product formulation are commonly used in oral solid dosage forms and the amounts are within the recommended daily intake limits. The drug product is tested for all the critical quality attributes (b) (4). The acceptance criterion for individual degradation product is NMT (b) (4)% which is below the ICH Q3B limits of 0.2%. The primary container closure for drug product consists of 100 mL and 120 mL HDPE bottle and a white child-resistant, (b) (4) screw cap with an aluminum induction seal and polyester coil is inserted on top of the filled tablets in the bottle. Applicant used a bracketing strategy (50 mg and 900 mg strengths) to support the shelf life for the 300 mg commercial dosage strength. The proposed shelf life of 36 months is supported by primary registration batches (50 mg and 900 mg) and supportive stability batches (300 mg) at the proposed storage condition of (b) (4) 30 °C, is acceptable.

C. Special Product Quality Labeling Recommendations: None

***D.* Life Cycle Knowledge Information:** None

Application Technical Lead Name and Date: Dhanalakshmi Kasi, Ph.D.

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate with revisions provided below.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	OXBRYTA® (voxelotor) tablets for oral suspension	Adequate
Established name(s)		
Route(s) of administration		
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tablets for oral suspension: 300 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.		

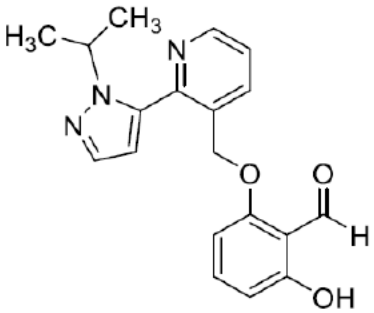
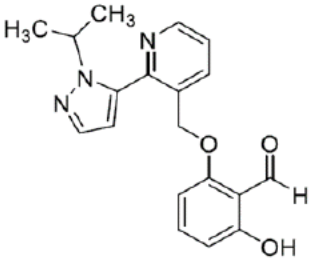
1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

<table>
<tr><th>Item</th><th>Information Provided in the NDA</th><th>Assessor's Comments</th></tr>
<tr><td colspan="3">DOSAGE AND ADMINISTRATION section</td></tr>
<tr><td>Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)</td><td>OXBRYTA 300 mg Tablets for Oral Suspension
(b) (4)
<table><tr><th>Recommended Daily Dose</th><th>Number of Tablets for Oral Suspension</th><th>Minimum Recommended Volume of (b) (4)</th></tr><tr><td>300 mg</td><td>1</td><td>5 mL (1 teaspoon)</td></tr><tr><td>600 mg</td><td>2</td><td>10 mL (2 teaspoons)</td></tr><tr><td>900 mg</td><td>3</td><td>15 mL (3 teaspoons)</td></tr><tr><td>1200 mg</td><td>4</td><td>20 mL (4 teaspoons)</td></tr></table>After the tablets start to disintegrate, swirl the contents of the cup until the tablets are (b) (4) dispersed, wait 1 to 5 minutes, swirl the contents of the cup again, and then orally administer the contents of the cup.
Resuspend any residue left in the cup in more (b) (4) clear drink and administer. Repeat until no tablet residue is left in the cup.</td><td>OXBRYTA 300 mg Tablets for Oral Suspension
Patients should disperse tablets immediately before administration in room temperature clear liquid (such as drinking water or clear soda) before swallowing.
<table><tr><th>Recommended Daily Dose</th><th>Number of Tablets for Oral Suspension</th><th>Minimum Recommended Volume of (b) (4)</th></tr><tr><td>300 mg</td><td>1</td><td>5 mL (1 teaspoon)</td></tr><tr><td>600 mg</td><td>2</td><td>10 mL (2 teaspoons)</td></tr><tr><td>900 mg</td><td>3</td><td>15 mL (3 teaspoons)</td></tr><tr><td>1200 mg</td><td>4</td><td>20 mL (4 teaspoons)</td></tr></table>•After the tablets start to disintegrate, swirl the contents of the cup until the tablets are (b) (4) dispersed, wait 1 to 5 minutes, swirl the contents of the cup again, and then orally administer the contents of the cup.
•Resuspend any residue left in the cup in more clear drink and administer. Repeat until no tablet residue is left in the cup.</td></tr>
</table>

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Tablets for oral suspension: 300 mg light yellow to yellow, round shaped, debossed with "300 D" on one side.	Adequate
Strength(s) in metric system		
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance		
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting		
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.		

Item		Assessor's Comments
DESCRIPTION:		
Proprietary and established name(s)	[redacted] a hemoglobin S polymerization inhibitor.	OXBRYTA contains voxelotor, a hemoglobin S polymerization inhibitor.
Dosage form(s) and route(s) of administration	The chemical name of voxelotor is: 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde.	The chemical name of voxelotor is 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde with a molecular formula of C19H19N3O3 and a molecular weight of 337.4.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	[redacted] a molecular formula of C19H19N3O3 and a molecular weight of 337.4.	The chemical structure of voxelotor is:
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	The chemical structure of voxelotor is: 	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Voxelotor, [redacted], is a white-to-yellow-to-beige compound in crystalline Form II of its free base. It is non-hygroscopic [redacted] highly soluble in common organic solvents such as acetone and toluene and insoluble in water [redacted].	Voxelotor, is a white-to-yellow-to-beige compound in crystalline Form II of its free base. It is non-hygroscopic and highly soluble in common organic solvents such as acetone and toluene and insoluble in water.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Each OXBRYTA tablet for oral suspension contains 300 mg of voxelotor with the following inactive ingredients: artificial grape flavor, colloidal silicon dioxide, croscarmellose sodium, iron oxide pigment, magnesium stearate, microcrystalline cellulose, and sucralose.	Each OXBRYTA tablet for oral suspension contains 300 mg of voxelotor with the following inactive ingredients: artificial grape flavor, colloidal silicon dioxide, croscarmellose sodium, iron oxide pigment, magnesium stearate, microcrystalline cellulose, and sucralose.
Statement of being sterile (if applicable)		
Pharmacological/ therapeutic class		
Chemical name, structural formula, molecular weight		
If radioactive, statement of important nuclear characteristics.		
Other important chemical or physical properties (such as pKa or pH)		

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	None.	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	None.	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) Strength(s) in metric system Available units (e.g., bottles of 100 tablets) Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored" For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	The 300 mg tablet for oral suspension is light yellow to yellow, round shaped, debossed with "300 D" on one side, and available in: • Bottles of 60 tablets for oral suspension with a polyester coil and child-resistant closure: NDC 72786-111-02 • Bottles of 90 tablets for oral suspension with a polyester coil and child-resistant closure: NDC 72786-111-03 Do not eat the desiccant canister or the polyester coil. (b) (4)	The 300 mg tablet for oral suspension is light yellow to yellow, round shaped, debossed with "300 D" on one side, and available in: •Bottles of 60 tablets for oral suspension with a polyester coil and child-resistant closure: NDC 72786-111-02 •Bottles of 90 tablets for oral suspension with a polyester coil and child-resistant closure: NDC 72786-111-03 Do not eat the desiccant canister or the polyester coil. (b) (4)

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

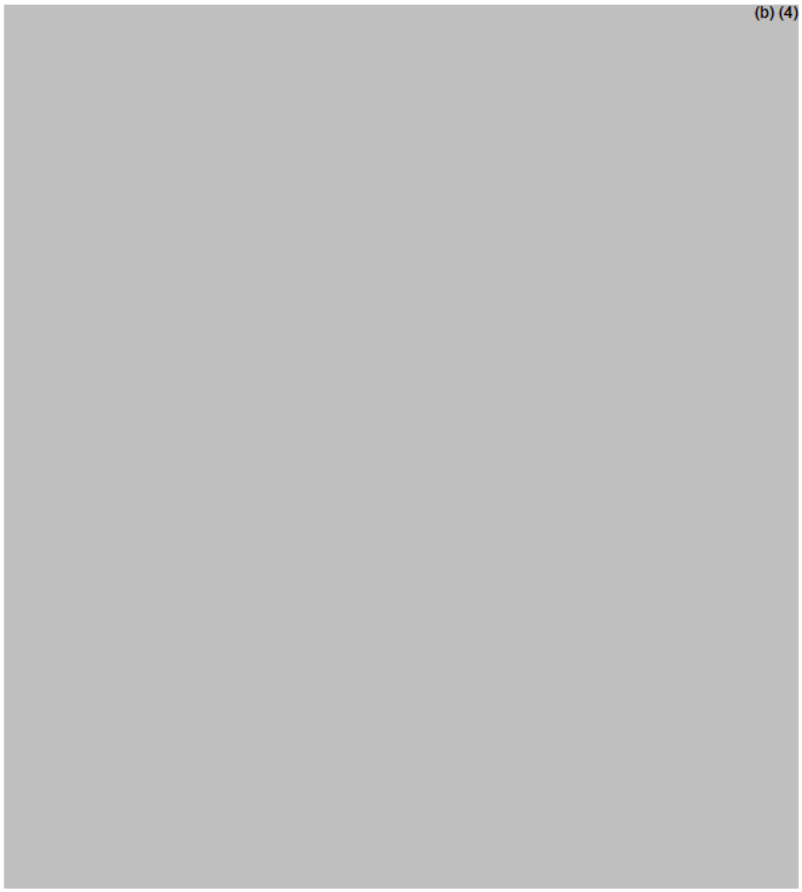
Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	N/A	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	See above.	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	
Include information about child-resistant packaging	No Information included.	

1.2.3 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Global Blood Therapeutics, Inc. South San Francisco, CA 94080 USA	Adequate

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label



3.2 Carton Labeling

No carton is used for this drug product.

Overall Assessment and Recommendation:

The labeling/labels will be adequate from a quality perspective after the recommended changes have been made.

Dhanalakshmi Kasi

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Date: 11/15/2021 09:20:43AM
GUID: 53150dea000054615f30e13bde0d487c

Mohan Sapru

Digitally signed by Mohan Sapru
Date: 11/15/2021 10:16:51AM
GUID: 504f821600000ec6d20b59d2b68eb3d2

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CHAPTER VI: BIOPHARMACEUTICS

For more details about the items in this template, please see Chapter VI (Biopharmaceutics) of the NDA IQA Guide

Product Information	
NDA Number	216157
Assessment Cycle Number	1
Drug Product Name/ Strength	Oxbryta (voxelotor) tablets for oral suspension, 300mg
Route of Administration	Oral
Applicant Name	Global Blood Therapeutics, Inc.
Therapeutic Classification/ OND Division	OCHEN/DNH
LD Number	N/A, 505 (b) (1) NDA
Proposed Indication	For the treatment of sickle cell disease in pediatric patients 4-11 years old

Assessment Recommendation: **Adequate**

Assessment Summary:

Voxelotor drug substance has low aqueous solubility. The composition of the proposed dispersible tablets is similar to that of the currently approved voxelotor tablet (F2) under NDA 213137, except for (b) (4) . The Applicant proposed to use the same dissolution method that was approved for the oral tablet. Because the proposed tablet for suspension contains similar inactive ingredients as the oral tablet, exhibits more rapid dissolution under same condition, and is shown to be bioequivalent to the oral tablets, the biopharmaceutics risk is reduced compared to the oral tablet formulation. Therefore the proposed dissolution method is acceptable for quality control. The dissolution acceptance criterion was tightened as per FDA recommendation to further mitigate the risk.
From a Biopharmaceutics perspective, NDA 216157 for Oxbryta (voxelotor) tablets for oral suspension, 300mg, is adequate and recommended for APPROVAL.
The FDA approved dissolution method and acceptance criterion are summarized in the Table below.

Apparatus	Speed	Medium	Volume	Temperature	Acceptance criterion
USP Apparatus 2 (Paddle)	75 rpm	2.0% SLS in 50 mM phosphate buffer, pH 6.8	900 mL	37 °C	Q= (b) (4) % in 15 min

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Dissolution	Medium	Voxelotor is a low solubility drug substance	Low	Implementation of appropriate dissolution method and acceptance criterion for routine QC testing of the proposed drug product mitigates the risk.

List of Submissions Being Assessed:

Document(s) Assessed	Date Received
Original NDA	06/25/2021
Response to CMC IR	07/22/2021
Response to CMC IR	07/30/2021
Response to Biopharmaceutics IR	10/08/2021

Highlight Key Issues from Last Cycle and Their Resolution: None. First review cycle.

Concise Description of Outstanding Issues: None. The NDA is found adequate from a Biopharmaceutics perspective.

B.1 BCS DESIGNATION

Assessment:
Solubility: Low

Voxelotor drug substance has low aqueous solubility. Voxelotor drug substance has two pKa values (2.6 for pyridinium ion and 8.3 for phenol group). The solubility of voxelotor drug substance in aqueous media (at various pH values) and in simulated gastrointestinal fluids are shown in Table 1.

Table 1[1]. Solubility of Voxelotor in Different Aqueous Media at Room Temperature

Media	Solubility (mg/mL)
Water	0.032
pH 1.1 buffer[a]	1.06
pH 5.0 buffer[b]	0.030
pH 7.0 buffer[c]	0.032
pH 9.0 buffer[d]	0.091
FaSSIF[e]	0.043
FeSSIF[f]	0.16

Abbreviations: FaSSIF, fasted state simulated intestinal fluid; FeSSIF, fed state simulated intestinal fluid.

[a] 97 mM HCl and 50 mM KCl.

[b] 40 mM orthophosphate buffer.

[c] 50 mM orthophosphate buffer.

[d] 50 mM potassium borate buffer with 50 mM NaCl.

[e] FaSSIF is pH 6.5 in phosphate buffer (29 mM), with 106 mM NaCl, 3 mM sodium taurocholate, and 0.75 mM lecithin.

[f] FeSSIF is pH 5.0 acetate buffer (144 mM), with 203 mM NaCl, 15 mM sodium taurocholate, and 3.75 mM lecithin.

Permeability: Unknown

The Applicant noted that the drug substance has high permeability based on an in vitro study using a polarized monolayer of Madin Darby Canine Kidney MDR1. However, no Caco-2 cell permeability data were provided in the submission, which is the commonly employed in vitro permeability test method.

As per the approved labeling for NDA213137[2], following the administration of radiolabeled voxelotor, approximately 62.6% of the dose and its metabolites are excreted into feces (33.3% unchanged) and 35.5% in urine (0.08% unchanged).

Dissolution: Very Rapid

Voxelotor dispersible tablets exhibited very rapid dissolution (≥ (b) (4)% in 15 min) using the proposed dissolution method. See Section B.2. DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment of Dissolution Method: *Adequate*

Voxelotor dispersible tablets were developed for pediatric patients and are intended to be dispersed in clear fluids prior to oral administration for ease of swallowing. The composition of the dispersible tablets is similar to that of the currently approved commercial formulation 2 (F2) tablet, except for (b) (4)

[1] Table 4 of Pharmaceutical Development Report (Page 12). \\CDSESUB1\evsprod\nda216157\0001\m3\32-body-data\32p-drug-prod\voxelotor-tablet-(b) (4)\32p2-pharm-dev\32p2-pharmaceutical-development.pdf

[2] NDA 213137 labeling. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213137s000lbl.pdf

(b) (4)

.

Table 2[3]. Formula Comparison of Voxelotor Core Tablets (approved under NDA213137) and Dispersible Tablets

Ingredients/Formulation	F2 Core Tablet [a]	Dispersible Tablet
	% w/w	
Voxelotor	(b) (4)	
Microcrystalline cellulose		
Croscarmellose Na		
Magnesium stearate		
Sodium lauryl sulfate		
Sucralose		
Artificial grape flavor		
Iron oxide pigment		
Colloidal silicon dioxide		
Total	100.00	100.00

Abbreviations: NA, not applicable.
[a] Uncoated tablet core.

Based on the similarity in the formulation (b) (4) between voxelotor dispersible tablets and F2 tablets, the dissolution method development for the dispersible tablets leveraged the dissolution method conditions developed for the F2 tablets.

Dissolution Method Development[4]:

(b) (4)

[3] Table 1 of Dissolution Method Development Report (page 4).
[4] Dissolution Method Development Report. \\CDSESUB1\evsprod\nda216157\0001\m3\32-body-data\32p-drug-prod\voxelotor-tablet-(b) (4)\32p2-pharm-dev\32p2-attachment-dissolution.pdf
[5] Table 2 of Dissolution Method Development Report (page 5).

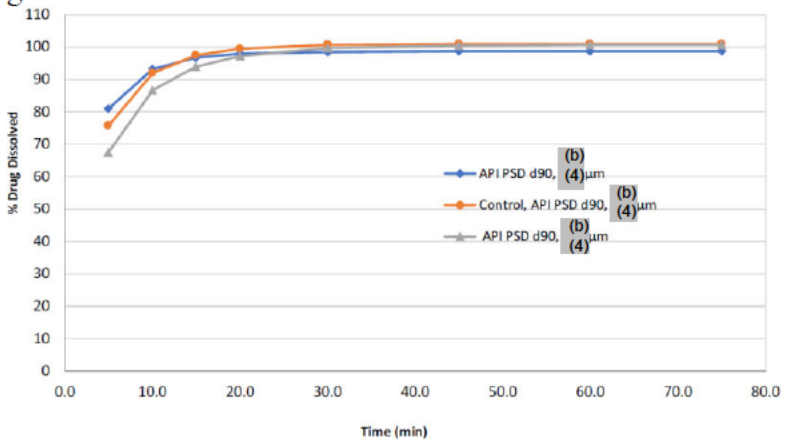
(b) (4)

Evaluation of Discriminating Ability of Method B:

Effect of Drug Substance Particle Size Distribution

R&D voxelotor dispersible tablets, 300 mg, were prepared with voxelotor drug substance at d90 values ranging from (b) (4) to (b) (4) µm. The range was selected to represent particles sizes that would comply with limit of d90 NMT (b) (4) µm defined in the voxelotor drug substance specification. The voxelotor drug substance originated as process validation and commercial batches. The dissolution profiles are shown in Figure 1. The Applicant noted that a negative correlation was observed between the dissolution rate and the particle size of voxelotor drug substance used in the dispersible tablets, though the differences are minor.

Figure 1[6]. Dissolution Profiles of Voxelotor Dispersible Tablets, 300 mg, Prepared with Voxelotor Drug Substance of Different Particle Sizes



Effect of (b) (4):

R&D voxelotor dispersible tablets, 300 mg, were prepared to produce (b) (4) ranging from (b) (4), including at the (b) (4) target for commercial production. The impact of tablet (b) (4) on the disintegration and the dissolution profile of voxelotor dispersible tablets, 300 mg, was evaluated. A positive correlation was observed between the disintegration time and the (b) (4) of the dispersible tablets (Table 4).

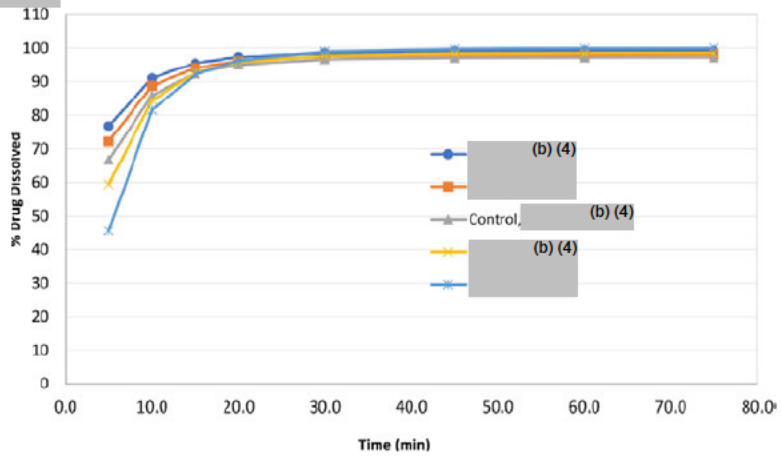
[6] Figure 1 of Dissolution Method Development Report (page 7).

Table 4[7]. Results of (b) (4) and Disintegration Time for Voxelotor Dispersible Tablets, 300 mg

Parameter	Result				
					(b) (4)
Disintegration Time (s)	17	34	48	45	115

A negative correlation was observed between the dissolution rate and the (b) (4) of the dispersible tablets, as shown in Figure 2.

Figure 2[8]. Dissolution Profiles of Voxelotor Dispersible Tablets, 300 mg, Prepared with Different (b) (4)



Effect of (b) (4) ***Content:***

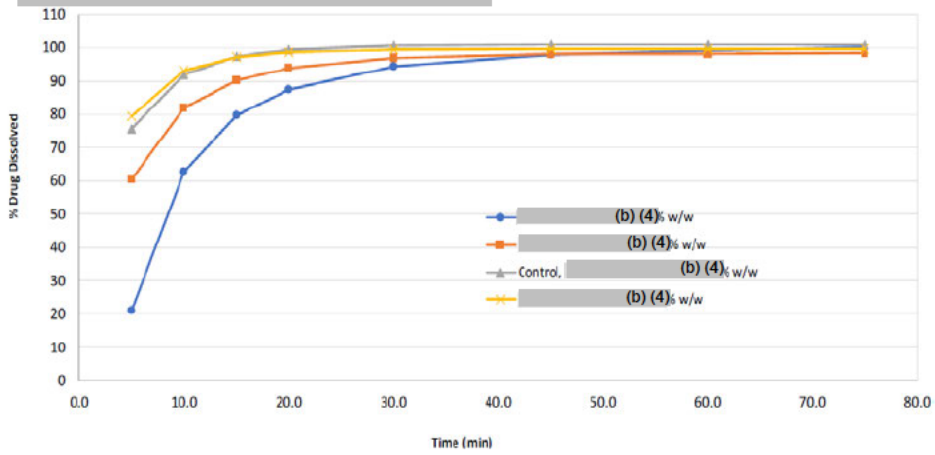
(b) (4), which is used commonly (b) (4) in a solid oral drug. R&D voxelotor dispersible tablets, 300 mg, were prepared to vary the (b) (4) content from (b) (4) % w/w, including at the (b) (4)% w/w target (as summation of (b) (4) content) for the commercial formulation. The effect of (b) (4) content differences on the disintegration time and dissolution profile of voxelotor dispersible tablets, 300 mg, was evaluated. A negative correlation was observed between the disintegration time and the (b) (4) content of the dispersible tablets, as shown in Table 5. A positive correlation was observed between the dissolution rate and the (b) (4) content of the dispersible tablets, as shown in Figure 3.

Table 5[9]. Disintegration Time for Voxelotor Dispersible Tablets, 300 mg, Prepared with Different (b) (4) Content

[7] Table 4 of Dissolution Method Development Report (page 7).
[8] Figure 2 of Dissolution Method Development Report (page 8).
[9] Table 5 of Dissolution Method Development Report (page 9).

Parameter	Result			
(b) (4) (% w/w)	(b) (4)			
Disintegration Time (s)	48	37	30	17

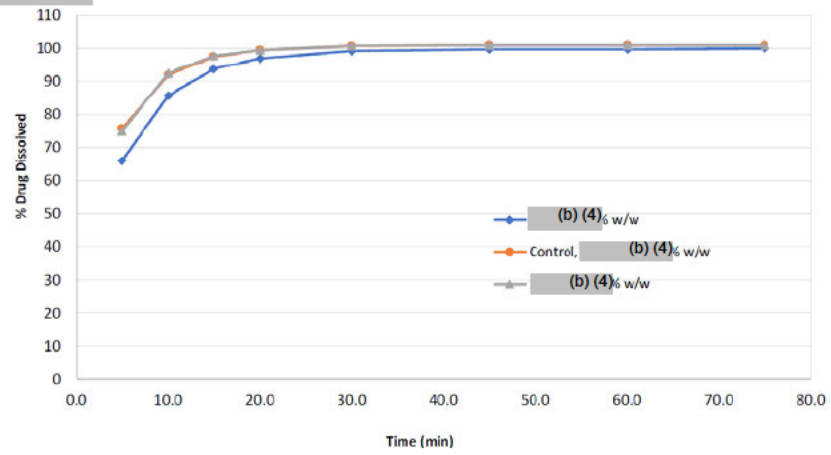
Figure 3[10]. Dissolution Profiles of Voxelotor Dispersible Tablets, 300 mg, Prepared with Different (b) (4) Content



Effect of (b) (4) Content:

(b) (4) is used as (b) (4) in the voxelotor dispersible tablet formulation. R&D voxelotor dispersible tablets, 300 mg, were prepared with (b) (4) content ranging from (b) (4) to (b) (4)% w/w, including the (b) (4)% w/w target for commercial production. As shown in Figure 4, the dissolution rate was similar for the (b) (4)% w/w and (b) (4)% w/w (b) (4) content. Slower dissolution was evident in the absence of (b) (4).

Figure 4[11]. Dissolution Profiles of Voxelotor Dispersible Tablets, 300 mg, Prepared with Different (b) (4) Content



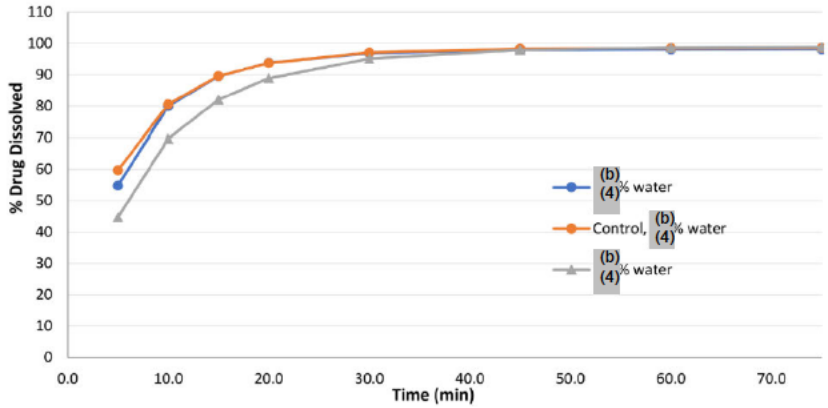
Effect of Water Content:

One lot of voxelotor dispersible tablets, 300 mg (cGMP Lot # CBXPT), was varied in water content from (b) (4)% to (b) (4)% by exposure of the drug product in an open dish to

[10] Figure 3 of Dissolution Method Development Report (page 9).
[11] Figure 4 of Dissolution Method Development Report (page 10).

heated or high relative humidity conditions. As shown in Figure 5, the dissolution rate was similar for dispersible tablets with (b) (4)% and (b) (4)% water content. Slower dissolution was evident for dispersible tablets with (b) (4)% water content.

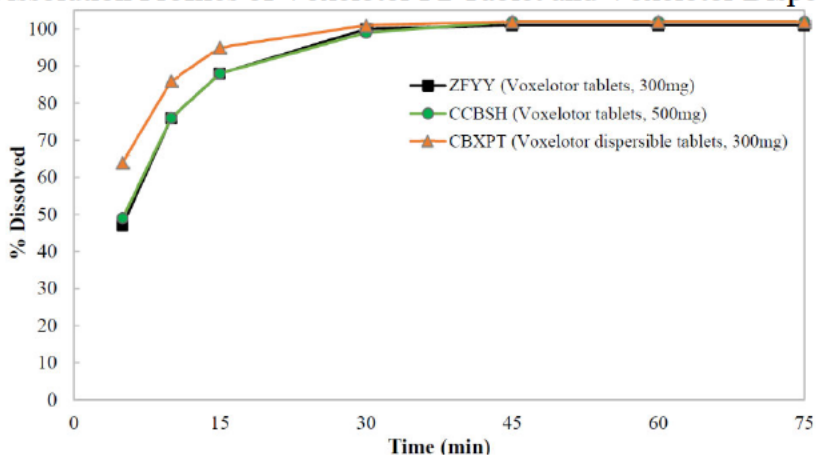
Figure 5. Dissolution Profiles of Voxelotor Dispersible Tablets, 300 mg, with Different Water Content



Dissolution Comparison to the Approved Tablet Formulation

The dissolution of the dispersible tablets is faster than the tablet formulation using the same dissolution method (2.0% (b) (4) in 50 mM (b) (4) phosphate at pH 6.8).

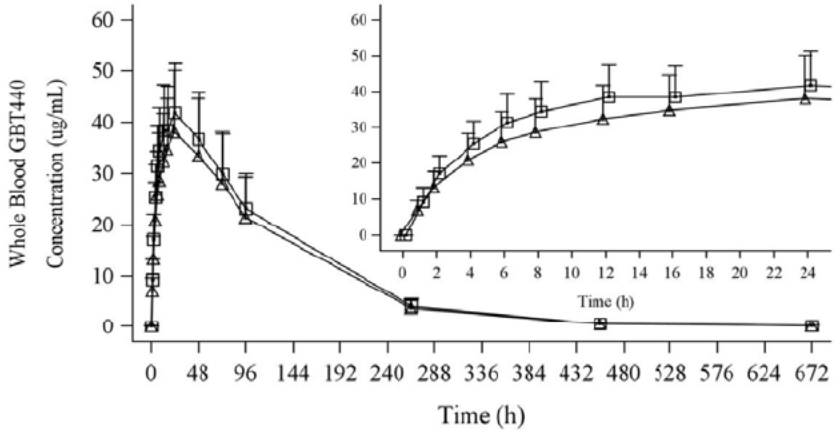
Figure 6[12]. Dissolution Profiles of Voxelotor F2 Tablet and Voxelotor Dispersible Tablet



The dispersible tablet is bioequivalent to the oral tablets (F1) based on an in vivo relative bioavailability study between 900mg dispersible tablet vs 3x300mg F1 tablets in healthy adults under fasted condition. F1 tablet is BE to F2 tablet, the approved commercial tablet formulation.

[12] Figure 1 of Summary of Biopharmaceutic Studies and Associated Analytical Methods- NDA213137-S006. \\CDSESUB1\evsprod\nda213137\0070\m2\27-clin-sum\summary-biopharm.pdf

Figure 7[13] Mean (+ SD) Whole Blood GBT440 Concentration-time Profiles (Open triangle: 900mg dispersible tablet; open square: 3x300mg F1 tablet)



Assessment of Dissolution Method: *Adequate*

Based on the similarity in formulation of the proposed tablet for suspension and the approved oral tablets, the Applicant proposed to use the same dissolution method that was approved for the oral tablet. The discriminating ability of the dissolution method against variations in the tablet formulation, (b) (4), drug substance particle size, and water content, was investigated, but limited discriminating power was observed based on the data.

Due to the low solubility of the drug substance, particle size can be a critical bioavailability attribute (CBA) of the drug product. As shown in Figure 1, product manufactured with drug substance at d90 values varying from (b) (4) to (b) (4) µm did not impact dissolution significantly. In addition, based on the information submitted to NDA213137 for the oral tablet formulation, dissolution profiles obtained using the same method are similar between the drug product lots manufactured with DS PSD of d90= (b) (4) µm and d90= (b) (4) µm[14], indicating lack of discriminating ability of the method against DS PSD.

Considering the proposed tablets for suspension contain similar inactive ingredients as the oral tablet, exhibit more rapid dissolution under same condition, and are shown to be bioequivalent to the oral tablets, the biopharmaceutics risk is reduced compared to the oral tablet formulation. The proposed dissolution method, which is the same as the method approved for the oral tablet, is acceptable for quality control.

Dissolution Acceptance Criterion:

[13] Page 25 of CSR GBT440 \\CDSESUB1\evsprod\NDA213137\0003\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\gbt440-0113\gbt440-0113-report-body.pdf

[14] Biopharmaceutics review for NDA213137-Orig-1. https://panorama.fda.gov/internal/document/preview?versionID=5d9b6323001654bd07ce5d1d1a554073&ID=5d937507000a7212e6d25863130ed39c

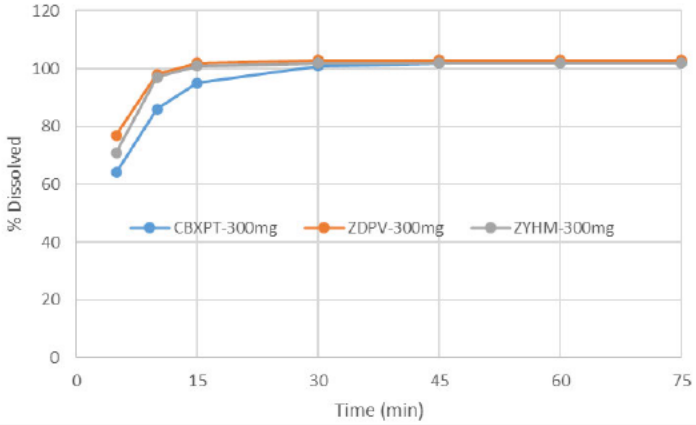
Assessment of Acceptance Criterion: *Adequate*

The batches of the dispersible tablets that were used in the clinical safety and efficacy studies in pediatric subjects are shown below[15]:

Study Report No.	Description	Phase	Study Population	Formulation, Strength	Bulk Product Lot No.
CSR GBT440-007, Part C	Efficacy and safety study	2a	Pediatric subjects with SCD, 4 to 17 years	Dispersible tablets, 300 mg	CBXPT ZDPV ZYHM

The dissolution data for the clinical batches in the table above are plotted in Figure 8[16].

Figure 8. Dissolution profiles of the clinical batches



Assessment of Acceptance Criterion: *Adequate*

Based on the dissolution data for the clinical batches, the Applicant was recommended to tighten the acceptance criterion to "Q= (b) (4)% in 15 min" through an Information Request dated 10/01/2021[17]. The Applicant agreed to the recommendation, and updated the dissolution acceptance criterion and relevant sections of the submission accordingly[18]. The updated acceptance criterion is acceptable.

[15] Table 2 of Summary of Biopharmaceutic Studies and Associated Analytical Methods- NDA213137-S006. \\CDSESUB1\evsprod\nda213137\0070\m2\27-clin-sum\summary-biopharm.pdf

[16] Reviewer's plot based on batch analysis data. \\CDSESUB1\evsprod\nda216157\0001\m3\32-body-data\32p-drug-prod\voxelotor-tablet-(b) (4)\32p5-contr-drug-prod\32p54-batch-analys\32p54-batch-analyses.pdf

[17] Biopharmaceutics IR dated 10/01/2021. APPENDIX 1 of this review.

[18] Response to Biopharmaceutics IR, received on 10/08/2021. \\CDSESUB1\evsprod\nda216157\0008\m1\us\response-20211001-rfi.pdf

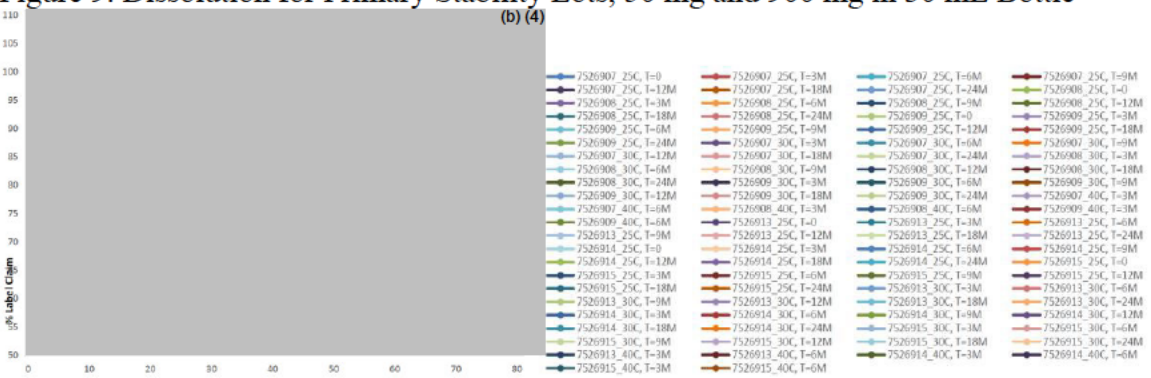
B.12 BRIDGING OF FORMULATIONS

Assessment: *Adequate*

During the drug product development, Voxelotor dispersible tablets, 100 mg and 300 mg, were developed for clinical studies. Voxelotor dispersible tablets, 900 mg, were developed for a relative BA study and were used in the primary stability study. Voxelotor dispersible tablets, 50 mg, were also developed and used for the primary stability study. Voxelotor dispersible tablets are manufactured with (b) (4), and the composition across different strengths is proportional[19]. All dispersible tablet strengths have the same formulation and the same ratio of the active ingredient to excipients. Furthermore, the manufacturing process and controls used in the manufacture of all dispersible tablet strengths were the same[20].
The clinical batches were manufactured using the proposed commercial manufacturing process[21] at the pilot scale ((b) (4) kg for Lots ZDPV and ZYHM) and larger ((b) (4) kg for Lot CBXPT) at the proposed commercial manufacturing site ((b) (4)). The proposed commercial production scale is (b) (4) kg[22].

The dissolution profiles of the 50mg, 300mg, and 900mg voxelotor dispersible tablets were similar to that of the 300mg dispersible tablets; the tablets exhibited very rapid dissolution with more than (b) (4)% dissolution in 15 min and all conformed to the recommended dissolution acceptance criterion.

Figure 9. Dissolution for Primary Stability Lots, 50 mg and 900 mg in 30 mL Bottle[23]



Assessment: *Adequate*

[19] Voxelotor Dispersible Tablet Strengths and Composition. Page 33. \\CDSESUB1\evsprod\nda216157\0001\m3\32-body-data\32p-drug-prod\voxelotor-tablet-(b) (4)\32p2-pharm-dev\32p2-pharmaceutical-development.pdf
[20] Response to Question 2. \\CDSESUB1\evsprod\nda216157\0003\m1\us\rsp-cmc-stability-20210721.pdf
[21] Response to Question 3. \\CDSESUB1\evsprod\nda216157\0004\m1\us\rsp-cmc-23jul2021.pdf
[22] QOS. \\CDSESUB1\evsprod\nda216157\0001\m2\23-qos\drug-product-voxelotor-tablet-(b) (4).pdf
[23] Figure 2 on Page 8 of 32P56. \\CDSESUB1\evsprod\nda216157\0008\m3\32-body-data\32p-drug-prod\voxelotor-tablet-(b) (4)\32p5-contr-drug-prod\32p56-justif-spec\32p56-justification-of-specifications.pdf

There is no difference in formulation, manufacturing process between the proposed commercial production and clinical lots, and the scale difference is less than 10-fold. The batches of the different strengths exhibited very rapid dissolution and conformed to the FDA recommended acceptance criterion. No additional bridging data is needed, provided the commercial lots comply with the drug product specifications.

B. 13 BIOWAIVER REQUEST

Assessment: *N/A*

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.

Primary Biopharmaceutics Assessor's Name and Date: Jing Li, Ph.D., 10/12/2021

Secondary Assessor Name and Date (and Secondary Summary, as needed): Poonam Delvadia, Ph.D., 10/13/2021

APPENDIX 1. Biopharmaceutics Information Request and the Applicant's Response

Biopharmaceutics IR Dated 10/1/2021:

Based on the information/data submitted, your proposed dissolution method is acceptable. However, the proposed dissolution acceptance criterion is permissive and not acceptable. We recommend that you implement the acceptance criterion of "Q= (b) (4)% in 15 min" for your proposed voxelotor tablets for oral suspension, as supported by the batch analysis data of the clinical lots.

Applicant's Response Received on 10/08/2021:

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Jing Li

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Poonam Delvadia

Digitally signed by Poonam Delvadia
Date: 10/13/2021 02:16:00PM
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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DHANALAKSHMI KASI
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