

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**213137Orig1s000**

**PRODUCT QUALITY REVIEW(S)**

**Recommendation: APPROVAL**

**NDA 213137  
Review #1**

Drug Name/Dosage Form	Oxbryta (Voxelotor) Tablets
Strength	500 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Global Blood Therapeutics, Inc
US agent, if applicable	N/A

SUBMISSIONS REVIEWED	DOCUMENT DATE
Original	26-JUN-2019
Amendment (SD 12)	25-JUL-2019
Amendment (SD 17)	26-AUG-2019
Amendment (SD 19)	28-AUG-2019
Amendment (SD 21)	04-SEPT-2019
Amendment (SD 22)	09-SEPT-2019
Amendment (SD 23)	11-SEPT-2019
Amendment (SD 28)	25-SEPT-2019

DISCIPLINE	REVIEWER/SECONDARY
Drug Substance	Gaetan Ladouceur/Su Tran
Drug Product	Nina Ni/Anamitro Banerjee
Process/Facility	Abdullah Mahmud/Bogdan
Microbiology	n/a
Biopharmaceutics	Mei Ou/Banu Zolnik
Regulatory Business Process Manager	Rabiya Haider
Application Technical Lead	Sherita McLamore
Environmental Analysis	James Laurenson

**Quality Review Data Sheet**

**1. RELATED/SUPPORTING DOCUMENTS**

**A. DMFs:**

DMF #	Type	Holder	Item Referenced	Status	Date Review	Comments
(b) (4)	Type III		(b) (4)	Not Reviewed	n/a	Sufficient information provided in NDA
	Type III			Not Reviewed	n/a	Sufficient information provided in NDA
	Type III			Not Reviewed	n/a	Sufficient information provided in NDA

**B. Other Documents: *IND, RLD, or sister applications***

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	121691	Voxelotor

**2. CONSULTS**

None.

## Executive Summary

### I. Overall Recommendation on Approvability

OPQ recommends **APPROVAL** of NDA 213137 for commercialization of Voxelotor Tablets, 500 mg, with an expiration dating period of 24 months:

- The applicant has provided adequate information on the proposed drug substance and drug product to ensure the identity, strength, purity and strength of the proposed drug product.
- The Office of Process and Facility has made a recommendation of approval for all the facilities involved in this application.
- The proposed labeling and labels have adequate information to meet the regulatory requirements.

### II. Product Quality Review Context

NDA 213137 was submitted as a 505(b)(1) NDA under the Federal Food, Drug and Cosmetic Act for Voxelotor Tablets, 500 mg. Voxelotor is a once daily, orally bioavailable, small-molecule, hemoglobin S polymerization inhibitor that is indicated for the treatment of sickle cell disease (SCD) in adult (b) (4) patients. Sickle cell disease is a serious group of blood disorders that affects hemoglobin. SCD is most prevalent among people of African descent and patients with SCD have an average life expectancy of 40 to 60 years. People with SCD have atypical hemoglobin molecules called hemoglobin S, which can distort red blood cells into a sickle shape. As a result of SCD, a number of health problems such as attacks of pain ("sickle cell crisis"), anemia, swelling in the hands and feet, bacterial infections and stroke may develop. There is currently no cure for SCD and treatment options are limited to hydroxy urea and/or L-Glutamine.

Voxelotor is a new molecular entity (NME) that was granted Fast Track designation (October 2015); Orphan Designation (December 2015); Rare Pediatric Disease Designation (Jun 2017); and Breakthrough Therapy Designation (January 2018). This product was also given PRIME designation by the EMA in June 2018. Voxelotor is a small, achiral, BCS Class 2 molecule, that is manufactured by (b) (4). The drug product is presented as 500 mg immediate-release solid oral dosage form and is formulated as a light yellow to yellow, biconvex, oval-shaped, film-coated, tablet with "GBT 500" debossed on one side.

Voxelotor is to be administered alone or in combination with hydroxyurea. The recommended dosing regimen for Voxelotor Tablets is 1500 mg taken orally once daily with or without food and 1000 mg taken orally once daily in patients with severe hepatic impairment (Child Pugh C) until disease progression or unacceptable toxicity.

<b>Proposed Indication(s) including Intended Patient Population</b>	Indicated for the treatment of sickle cell disease (SCD) in adult (b) (4) patients
<b>Duration of Treatment</b>	Chronic administration, once daily
<b>Maximum Daily Dose</b>	1500 mg

<b>Alternative Methods of Administration</b>	N/A
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### III. Summary of Quality Assessments

The following is a summary of key assessments from the reviews of drug substance, drug product, manufacturing, and biopharmaceutics found in the respective technical chapters for each discipline. A summary of the assessments is provided in this section. Section IV further discusses key review issues in greater detail.

Voxelotor is a small achiral BCS class 2 molecule that is produced as a white to yellow to beige non-hygroscopic crystalline solid. It is practically insoluble in water and is freely soluble in toluene.

Voxelotor is manufactured by (b) (4) in (b) (4). The applicant included the (b) (4) and identified critical quality attributes (CQAs) and critical process parameters (CPPs). The applicant (b) (4)

(b) (4)

The applicant included 24 months long term (25 C/60%RH) 6 months of accelerated (40 C/75%RH) stability data for three primary stability batches in support of the proposed (b) (4) retest period for the drug substance when stored under controlled room temperature. The provided data were adequate to support the proposed re-test period and as such the (b) (4) re-test period is granted. The proposed drug substance specification is consistent with ICH Q6A and includes testing for appearance, identification, polymorphic form, related substance, residual solvents, (b) (4), residue on ignition and particle size. The original acceptance criterion of the particle size was d<sub>90</sub> NMT (b) (4) µm (see issue 1 in Section IV for further discussion). The drug substance specifications were deemed adequate to ensure that the critical quality attributes of the drug substance in the tablet formulation are well controlled.

The drug product is presented as a 500-mg immediate-release solid oral dosage form. It is formulated as a light yellow to yellow, biconvex, oval-shaped, film-coated, immediate-release tablet with “GBT 500” debossed on one side. The drug product formulation includes the active together with excipients that are commonly used in solid oral formulations. All excipients with the exception of the (b) (4) film-coating system (which consists of compendial excipients) are compendial.

The QTPP for the drug product was established based on the properties of the drug substance, characteristics of the drug product and the intended patient population. The CQAs which were identified based on the QTPP include appearance, identification, assay, content uniformity,

degradation products, dissolution, microbial limits, (b) (4), and elemental impurities. The drug product is manufactured by (b) (4) at a commercial batch size of ca. (b) (4) kg which corresponds to ca. (b) (4) tablets. The drug product manufactured with a high loading dose using standard methodology.

Throughout development, two different solid oral dosage forms were used: capsules and tablets. The capsule formulation included a 100 mg powder in capsule (PIC) formulation and two 300 mg (b) (4) formulations ((b) (4)). The (b) (4) formulation contained a (b) (4). The tablet dosage form included two slightly different formulations (F1 and F2). F2 differs from F1 by the (b) (4)

Three F2 tablet dosage strengths (300 mg, 500 mg and 900 mg) were developed from a (b) (4). A comparison of formulation compositions for F1 tablet and F2 tablet at different strengths included in the table below. The 300 mg tablets were used for Phases 1, 3 and 4 clinical studies, the 900 mg tablet was used in the rBA and the 500 mg tablet is the proposed commercial product. The biopharmaceutics reviewer concluded that no additional *in vitro* bridging studies were needed since the commercial formulation is compositionally proportional to the 300 mg formulation used in the pivotal Phase 3 safety and efficacy studies.

The applicant studied the stability of these tablets using a bracketing approach and requested a 24-month expiry for the drug product when stored in the commercial container closure system at or below 30 C. In support of the requested expiry the applicant provided 12 months of primary data for three batches each of the 300 and 900 mg tablets. The stability studies were executed in accordance with the ICH 1A and Q1B, and the available stability data shows consistency over time with no notable trends under any storage condition. Therefore, based on the stability data provided, Global Blood Therapeutics, Inc. proposed and the FDA accepts the expiration dating period of **24 months** for the drug product when stored at stored at or below 30 C (86 F).

The final risk assessment is low for all unit operations and the applicant has provided adequate in-process controls for consistent batch to batch product quality. Following a review of the application and inspectional documents, there are no significant, outstanding manufacturing risks that prevent approval of this application. Based on the inspectional history, inspection report reviews, and district office recommendation, the manufacturing facilities listed were ultimately deemed acceptable for the responsibility listed in the application (see Issue 2).

The proposed container labels meet all regulatory requirements from a CMC perspective. Review and revision of the prescribing information, MedGuide, and any other associated patient labeling will be conducted in collaboration with the clinical division.

*The claim for categorical exclusion is granted in accordance with 21 CFR 25.15(b).*

#### **IV. Final Analysis of Product Quality Review Issues**

In the product quality review of this NDA, two issues were identified as having potential significance on the evaluation of the product's efficacy, safety, or availability and thus warranted a more thorough analysis of their potential impact on patients and any implications on OPQ's regulatory recommendations.

##### **Issue #1: PARTICLE SIZE ACCEPTANCE CRITERION**

At the time of submission, the proposed acceptance criterion for the particle size was  $D_{90}$  (b) (4)  $\mu\text{m}$  based on the analysis from the clinical batches made from the commercial site. The review team concluded that the proposed (b) (4)

### **Key Evidence/Uncertainties**

While evaluating the discriminating ability of the dissolution method, the applicant manufactured Oxbryta tablets with formulation variations, different drug substance particle sizes, and different tablet hardness. Review of the data revealed that (b) (4)

Additional data provided in support of the proposed particle size acceptance criterion of  $D_{90}$  (b) (4)  $\mu\text{m}$  demonstrated that tablets manufactured with drug substance PSD  $D_{90}$  (b) (4)  $\mu\text{m}$  had similar dissolution to the target lot ZFYV that had a PSD  $D_{90}$  (b) (4)  $\mu\text{m}$ . From this data it appeared that proposed dissolution method was not discriminating with respect to PSD and that drug substance of particle size up to  $D_{90} =$  (b) (4)  $\mu\text{m}$  had no impact on the tablet physical properties or on the dissolution profile. The reviewer noted the apparent discrepancy and sent the following IR on 8/22/2019

*The proposed drug substance particle size distribution (PSD) limits for your product is not adequately justified. Based on the particle size of all drug substance batches submitted in the NDA, including the clinical batches and commercial batches, FDA recommends that you revise the drug substance PSD limit to  $D_{90}$  (b) (4)  $\mu\text{m}$ .*

The applicant responded, explained the discrepancy and proposed (b) (4) the PSD limit from  $D_{90}$  (b) (4)  $\mu\text{m}$  to  $D_{90}$  (b) (4)  $\mu\text{m}$ .

### **Conclusions**

Based on the applicant's response, this risk is sufficiently mitigated as the applicant explained the inconsistencies and revised the DS PSD acceptance criterion to be more in line with their manufacturing capability and should result in a final product that is more consistent and has less batch to batch variability.

### **Issue #2: TESTING FACILITY**

This application included the following 9 sites and all sites were listed as ready for inspection at the time of submission.

- **Global Blood Therapeutics, Inc. (no FEI number listed)**- Drug product: lot release for distribution of finished drug product

(b) (4)

With the exception of (b) (4) and Global Blood Therapeutics (GBT), all sites were approved based on previous history. The (b) (4) site was approved based on PAI; however, the GBT site was inspected during this review cycle and was issued a VAI (Voluntary Action Indicated) for method validation /method transfer failures (see Process and Facility Review).

### ***Key Evidence/Uncertainties***

The GBT site was inspected on 8/30/19 and the site was issued a VAI. The VAI would typically result in a withhold recommendation from OPF. As the site in question was only listed to perform the test for appearance, the team considered having the firm removing the (b) (4) site from the NDA to facilitate approval. Following the inspection, the lead investigator provided the following information:

- During inspection, it was concluded that the (b) (4) test was not completely validated. However, the investigator had no concerns about the test itself
- Nonetheless, the test (b) (4) was removed from the facility role in Amendment 0019 dated 08/28/2019 and only the Appearance test was to be conducted at this site
- The inspection field recommendation for the GMP only inspection is VAI

### ***Conclusions***

Based on the firm's updated role, OPF recommended approval the (b) (4) facility as the VAI recommendation does not necessitate a WITHHOLD for the site. Accordingly, there is no need for applicant to withdraw (b) (4) from the application and no additional concerns regarding the firm's ability to perform the duties outlined in the submission. .

## **V. Summary Basis for Product Quality Recommendation**

The applicant provided sufficient information to assure the identity, strength, purity, quality, and bioavailability of the proposed drug product. The key review issues (Section IV) have been adequately resolved and were deemed to have minimal likely impact on patient efficacy or safety and do not preclude approval of this product. The labels and labeling include adequate quality information as required. All associated manufacturing, testing, packaging facilities were deemed acceptable. Based on the OPQ review team's evaluation of the information provided in the submission, Oxbryta (Voxelotor) Tablets possess the necessary attributes to ensure that the product meets the quality target product profile (b) (4)

## **VI. Lifecycle Considerations**

There are no outstanding issues or lifecycle considerations and no post-approval quality agreements to be conveyed to the applicant.



Sherita  
McLamore

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## CHAPTER IV: LABELING

### 1.0 PRESCRIBING INFORMATION

#### Assessment of Product Quality Related Aspects of the Prescribing Information:

#### 1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
<b>Product Title in Highlights</b>		
Proprietary name	Tradename	Provided and adequate
Established name(s)	Voxelotor	Provided and adequate
Route(s) of administration	For oral use	Added and adequate
<b>Dosage Forms and Strengths Heading in Highlights</b>		
Summary of the dosage form(s) and strength(s) in metric system.	Tablets: 500 mg	Provided and adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA, the tablet is not 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.	NA	NA

### 1.2 FULL PRESCRIBING INFORMATION

**1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)**

Item	Information Provided in the NDA	Assessor's Comments
<b>DOSAGE AND ADMINISTRATION section</b>		
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)	1500 mg taken once daily with or without food. The clinical pharmacology reviewer was asked whether the following is needed? "Swallow tablet whole. Do not crush, chew, or dissolve the tablet." Refer to the clinical pharmacology review for the evaluation of this issue.	Provided and adequate

**1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)**

Item	Information Provided in the NDA	Assessor's Comments
<b>DOSAGE FORMS AND STRENGTHS section</b>		
Available dosage form(s)	Tablets	Provided and adequate
Strength(s) in metric system	500 mg	Provided and adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Per free base	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Light yellow to yellow, oval shaped, biconvex, debossed with "GBT 500" on one side	Provided and adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA, the tablet is not 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.	NA	NA

### 1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
<b>DESCRIPTION section</b>		
Proprietary and established name(s)	Tradename and Voxelotor	Provided
Dosage form(s) and route(s) of administration	Each Tradename (voxelotor) film-coated tablet for oral use contains...	Added and adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Yes, the strength is based on free base	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	All inactive ingredients use USP/NF names	Adequate
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.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)	NA	NA
Pharmacological/ Therapeutic class	A hemoglobin S polymerization inhibitor	Provided and adequate
Chemical name, structural formula, molecular weight	Provided	Adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	Provided	Adequate

**Section 11 (DESCRIPTION) Continued**

<b>Item</b>	<b>Information Provided in the NDA</b>	<b>Assessor's Comments</b>
For oral prescription drug products, include gluten statement if applicable	NA	NA
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	NA	NA

**1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)**

<b>Item</b>	<b>Information Provided in the NDA</b>	<b>Assessor's Comments</b>
<b>HOW SUPPLIED/STORAGE AND HANDLING section</b>		
Available dosage form(s)	Tablets	Added and adequate
Strength(s) in metric system	500 mg	Added and adequate
Available units (e.g., bottles of 100 tablets)	Bottle of 90 tablets	Provided and adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	light yellow to yellow, oval shaped, biconvex, debossed with "GBT 500" on one side NDC number provided	Added and adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	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.	NA	NA

**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.)	NA	NA
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."	The bottle also contains one desiccant canister and one polyester coil. Do not eat.	Added and adequate
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at or below 30°C (86°F)	Adequate
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."	NA	NA
Include information about child-resistant packaging	Included	Adequate

**1.2.5 Other Sections of Labeling**

NA

**1.2.6 Manufacturing Information After Section 17 (for drug products)**

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

## 2.0 PATIENT LABELING

**Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): Adequate**

***Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT." None***

## 3.0 CARTON AND CONTAINER LABELING

### 3.1 Container Label

Not provided. Lack of container label was conveyed to the DMEPA at the first labeling review meeting on 09/03/2019. Refer to the DMEPA's review for the evaluation of this issue.

### 3.2 Carton Labeling



Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	Oxbryta (voxelotor) tablets	Adequate Oxbryta is under review.
Dosage strength	500 mg	Adequate
Route of administration	Not provided	Adequate for oral dosage form
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	The strength is based on free base form	Adequate
Net contents (e.g. tablet count)	90 tablets	Adequate
"Rx only" displayed on the principal display	Provided	Adequate
NDC number	Provided	Adequate
Lot number and expiration date	Space allocated	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at or below 30°C (86°F).	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	NA
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Bar code	Provided	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Provided	Adequate
Medication Guide (if applicable)	NA	NA
No text on Ferrule and Cap over seal	Do not use if safety seal under cap is broken or missing	Adequate
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	NA	NA
And others, if space is available	NA	NA

**Assessment of Carton and Container Labeling:** {Adequate}

**Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."** None

## ITEMS FOR ADDITIONAL ASSESSMENT

None.

### Overall Assessment and Recommendation:

Adequate.

*Primary Labeling Assessor Name and Date: Nina Ni, Ph.D., 09/23/2019*

*Secondary Assessor Name and Date (and Secondary Summary, as needed): Anamitro Banerjee, Ph.D., 09/25/2019*



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**BIOPHARMACEUTICS****NDA: 213137 [505(b)(1)]****Drug Product Name/Strength:** Oxbryta (GBT440) Tablets, 500 mg**Route of Administration:** Oral**Applicant Name:** Global Blood Therapeutics, Inc.**Proposed Indication:** For the treatment of sickle cell disease in adults (b) (4)**Submission Dates:**

06/27/2019 (Original Submission)

08/26/2019 (Biopharmaceutics Information Request Response)

**Primary Reviewer:** Mei Ou, Ph.D.**Secondary Reviewer:** Banu Zolnik, Ph.D.**EXECUTIVE SUMMARY**

The proposed drug product, Oxbryta Tablet, 500 mg, is an immediate-release film-coated tablet for oral administration for the treatment of sickle cell disease in adults (b) (4). The proposed dosing regimen is 1500 mg once daily, or 1000 mg once daily in patients with severe hepatic impairment.

In the preliminary comments and meeting minutes of a Type B Teleconference cross reference to IND 121691 dated 12/12/2018<sup>1</sup> and 12/21/2018<sup>2</sup>, the Division of Biopharmaceutics: (a) considered the Applicant's approach of developing a dissolution method for quality control (QC) and stability testing appeared to be reasonable during IND stage; (b) conveyed the detailed recommendations of developing an appropriate dissolution QC method and setting the dissolution acceptance criterion; (c) requested the dissolution methods and data for all formulations that have been used in clinical studies.

In current NDA 213137 submitted on 06/27/2019, the Biopharmaceutics Review focuses on the evaluation of: i) the *in vitro* dissolution method and acceptance criterion of the proposed drug product, and ii) the need of *in vitro* bridging between the clinical and commercial formulations.

**In Vitro Dissolution Testing of the Finished Product:**

The proposed dissolution method showed an acceptable discriminating ability with regards to drug substance particle size distribution, (b) (4) and formulation (b) (4) variables, the proposed dissolution method is **acceptable** as a quality control (QC) test for the propose drug product for batch release and stability testing.

<sup>1</sup> [https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804cb341&\\_afRedirect=1709260872532724](https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804cb341&_afRedirect=1709260872532724)

<sup>2</sup> [https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804ce4f2&\\_afRedirect=1709277811812197](https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804ce4f2&_afRedirect=1709277811812197)

The final approved *in vitro* dissolution method and acceptance criterion for the finished drug product are presented below:

USP Apparatus	II (Paddle)
Rotation Speed	75 rpm
Medium and Volume	900 mL of 50 mM phosphate buffer, pH 6.8, with 2.0% SLS
Temperature	37°C ± 0.5°C
Acceptance Criterion	Q = <sup>(b)</sup> <sub>(4)</sub> % in 30 minutes

*In Vitro* Formulation Bridging:

The *in vivo* bioavailability/bioequivalence (BA/BE) studies (StudyGBT440-044, GBT440-018 and GBT440-0114) have been conducted using the clinical and commercial formulations. The adequacy of these studies is under purview of the Office of Clinical Pharmacology (OCP) (please refer to Clin. Pharm Review). Since the commercial formulation (500 mg tablets) is compositionally proportional to the pivotal formulation (300 mg) that have been used in pivotal Phase 3 safety and efficacy studies, no additional *in vitro* bridging studies between the clinical and commercial formulations are needed.

**RECOMMENDATION**

From the Biopharmaceutics perspective, NDA 213137 for the proposed Oxbryta (GBT440) Tablets, 500 mg, is recommended for **APPROVAL**.

**BIOPHARMACEUTICS REVIEW**

**1. Drug Substance Solubility and Permeability**

**Solubility:** The Applicant stated that the drug substance, Oxobryta (with two pKa values, 2.6 for pyridinium ion and 8.3 for phenol group), is a BCS II compound. As the solubility data presented in the following Tables 1 and 2 and Figures 1 and 2, the drug substance has low solubility (< 500 mg/250 ml = 2.0 mg/mL) in aqueous buffers from pH 1.1 to 9.0 and in water without surfactant.

Table 1: Solubility of Oxobryta Drug Substance in Different Aqueous Media at Room Temperature (data from M.3.2.P.2)

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

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

<sup>a</sup> 97 mM HCl and 50 mM KCl.

<sup>b</sup> 40 mM orthophosphate buffer.

<sup>c</sup> 50 mM orthophosphate buffer.

<sup>d</sup> 50 mM potassium borate buffer with 50 mM NaCl.

<sup>e</sup> FaSSIF is pH 6.5 in phosphate buffer (29 mM), with 106 mM NaCl, 3 mM sodium taurocholate, and 0.75 mM lecithin.

<sup>f</sup> FeSSIF is pH 5.0 acetate buffer (144 mM), with 203 mM NaCl, 15 mM sodium taurocholate, and 3.75 mM lecithin.

Table 2: Solubilities of Oxobryta in Different Media (data from M.3.2.P.2.2)

Buffer Composition	Temperature	Solubility (mg/mL)	USP Solubility	
pH 1.1 buffer (50 mM KCl and 97 mM HCl)	Room temperature	1.06	Slightly soluble	
pH 2.0 buffer (50 mM KCl and 11 mM HCl)		0.13	Very slightly soluble	
pH 3.0 buffer (80 mM citrate and 40 mM phosphate)		0.055	Insoluble	
pH 4.0 buffer (60 mM citrate and 80 mM phosphate)		0.040	Insoluble	
pH 5.0 buffer (40 mM orthophosphate)		0.030	Insoluble	
pH 6.0 buffer (37 mM citrate and 126 mM phosphate)		0.031	Insoluble	
pH 7.0 buffer (50 mM orthophosphate)		0.032	Insoluble	
1 × Phosphate Buffered Saline pH 7.4 <sup>a</sup>		0.041	Insoluble	
Water		0.051	Insoluble	
FaSSGF (pH 1.6) <sup>b</sup>		0.24	Very slightly soluble	
FeSSIF (pH 5.0) <sup>c</sup>		0.16	Very slightly soluble	
FaSSIF (pH 6.5) <sup>d</sup>		0.043	Insoluble	
36 mM Acetate buffer (pH 4.5)		37 °C	0.040	Insoluble
50 mM PB (pH 6.8)			0.032	Insoluble
50 mM PB (pH 6.8) with 0.3% SLS	0.62		Very slightly soluble	
50 mM PB (pH 6.8) with 0.5% SLS	1.09		Slightly soluble	
50 mM PB (pH 6.8) with 1.0% SLS	2.04		Slightly soluble	
50 mM PB (pH 6.8) with 2.0% SLS	3.82		Slightly soluble	
0.1 N HCl (pH 1.2)	1.01		Slightly soluble	
0.1 N HCl with 0.5% SLS (pH 1.2)	2.45		Slightly soluble	
0.1 N HCl with 0.5% Tween® 80 (pH 1.2)	1.25		Slightly soluble	
0.1 N HCl with 1.0 % Tween® 80 (pH 1.2)	1.45		Slightly soluble	

PB, sodium phosphate buffer.

<sup>a</sup> PBS (1X, pH 7.4) is 137 mM NaCl, 2.7 mM KCl, 10 mM Na<sub>2</sub>HPO<sub>4</sub>, and 1.8 mM KH<sub>2</sub>PO<sub>4</sub>.

<sup>b</sup> FaSSGF is pH 1.6 HCl buffer containing 34 mM NaCl, 0.08 mM taurocholate, and 0.02 mM phospholipids.

<sup>c</sup> FeSSIF is pH 5.0 acetate buffer (144 mM), with 203 mM NaCl, 15 mM sodium taurocholate, and 3.75 mM lecithin.

<sup>d</sup> FaSSIF is pH 6.5 phosphate buffer (29 mM), with 106 mM NaCl, 3 mM sodium taurocholate and 0.75 mM lecithin.

Figure 1: Solubility Profile of Oxbryta in Aqueous Solutions as a Function of pH at Room Temperature (data from M.3.2.P.2.2)

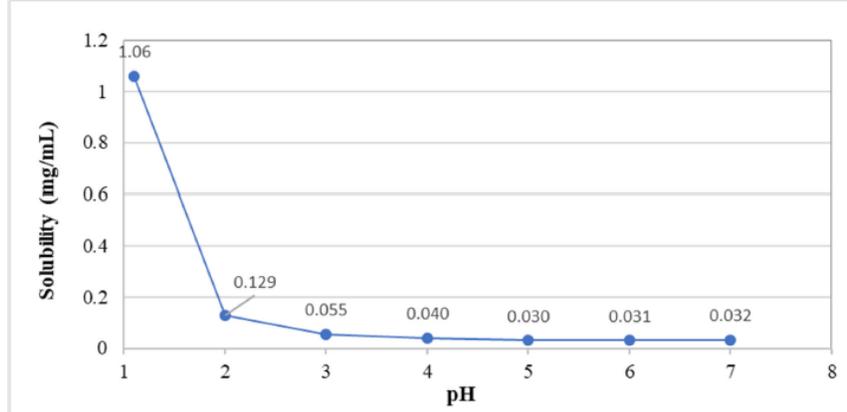
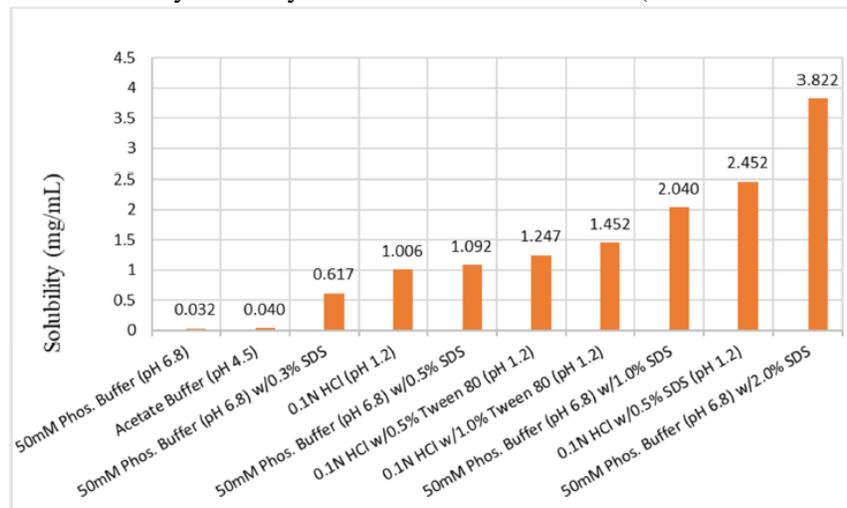


Figure 2: Solubility of Oxbryta in Various Media at 37°C (data from M.3.2.P.2.2)



**Permeability:** Per the Applicant, the apparent permeability ( $P_{app}$ ) values for Oxbryta drug substance from apical (A) to basal (B) (A-to-B) and B-to-A transport were  $1.16 \times 10^{-6}$  and  $1.52 \times 10^{-6}$  cm/sec, respectively, resulting in a  $P_{app}$  (B-to-A) /  $P_{app}$  (A-to-B) ratio of 1.31. These results suggested that Oxbryta drug substance has high permeability.

However, considering (i) this in vitro polarized monolayer of Madin Darby Canine Kidney MDR 1 (MDCK-MDR1) cells system (from study PRC-14-013-R) was used to study the drug-drug interaction (DDI), (ii) the comparator Digoxin is an Efflux Substrate but not a high or low permeability marker per FDA BCS guidance (December 2017), (iii) the absolute bioavailability of Oxbryta was not studied, but is estimated to be at least 35% based on data from a mass-balance study, per the Applicant, (iv) absolute oral bioavailability measured in whole blood ranged from 36% to 71% in mouse, rat, dog, and monkey, per the Applicant, therefore, this Reviewer considers that the determination of high permeability of the Oxbryta drug substance is still premature at this point. *Note that no BCS classification request of the drug substance and drug product is submitted for review in this NDA.*

**2. In Vitro Dissolution Method**

The proposed dissolution method and acceptance criterion as a quality control (QC) test for the drug product batch release and stability testing are summarized as below:

USP Apparatus	II (Paddle)
Rotation Speed	75 rpm
Medium and Volume	900 mL of 50 mM phosphate buffer, pH 6.8, with 2.0% SLS
Temperature	37°C ± 0.5°C
Acceptance Criterion	Q = <sup>(b)</sup> <sub>(4)</sub> % in 30 minutes

The Oxbryta tablets Formulation 1 (F1 300 mg) and Formulation 2 (F2 300 mg, 500 mg and 900 mg, *see the in vitro bridging review section below*) were used during dissolution method development. Note that F2 500 mg tablet is developed as the commercial drug product.

The following parameters have been evaluated during the dissolution method development, summarized as:



(b) (4)

Overall, the dissolution information and data of the commercial batch (500 mg) support the proposed dissolution acceptance criterion of “Q= (b) (4)% in 30 minutes”.

**4. Formulation Bridging**

Per the Applicant, Oxbryta has been developed in 2 oral solid dosage forms: capsules and tablets. Initially, 2 types of capsule dosage forms, Powder in Capsule (PIC) and (b) (4) were developed. The Oxbryta PIC formulation (50- and 100-mg capsules) was developed first and used in the early Phase 1 clinical studies in healthy subjects. Thereafter, to allow for higher drug loading, the (b) (4) capsule formations (b) (4) 300-mg capsules) were developed and used in subsequent Phase 1 clinical studies and in the Phase 2a clinical study GBT440-007 in adolescents with SCD. The Oxbryta tablet formulations (Formulation 1 [F1] and Formulation 2 [F2]; 300-mg tablets) were developed to enable manufacturing process improvement and to support potentially higher clinical doses in later-phase clinical studies, including the pivotal Phase 3 efficacy and safety study GBT440-031 in adults and adolescents with SCD. A 500-mg F2 tablet has been developed as the proposed commercial drug product for use in adults (b) (4) with SCD.

The summary of the Oxbryta formulations are presented in Table 9 and Figure 18 below.

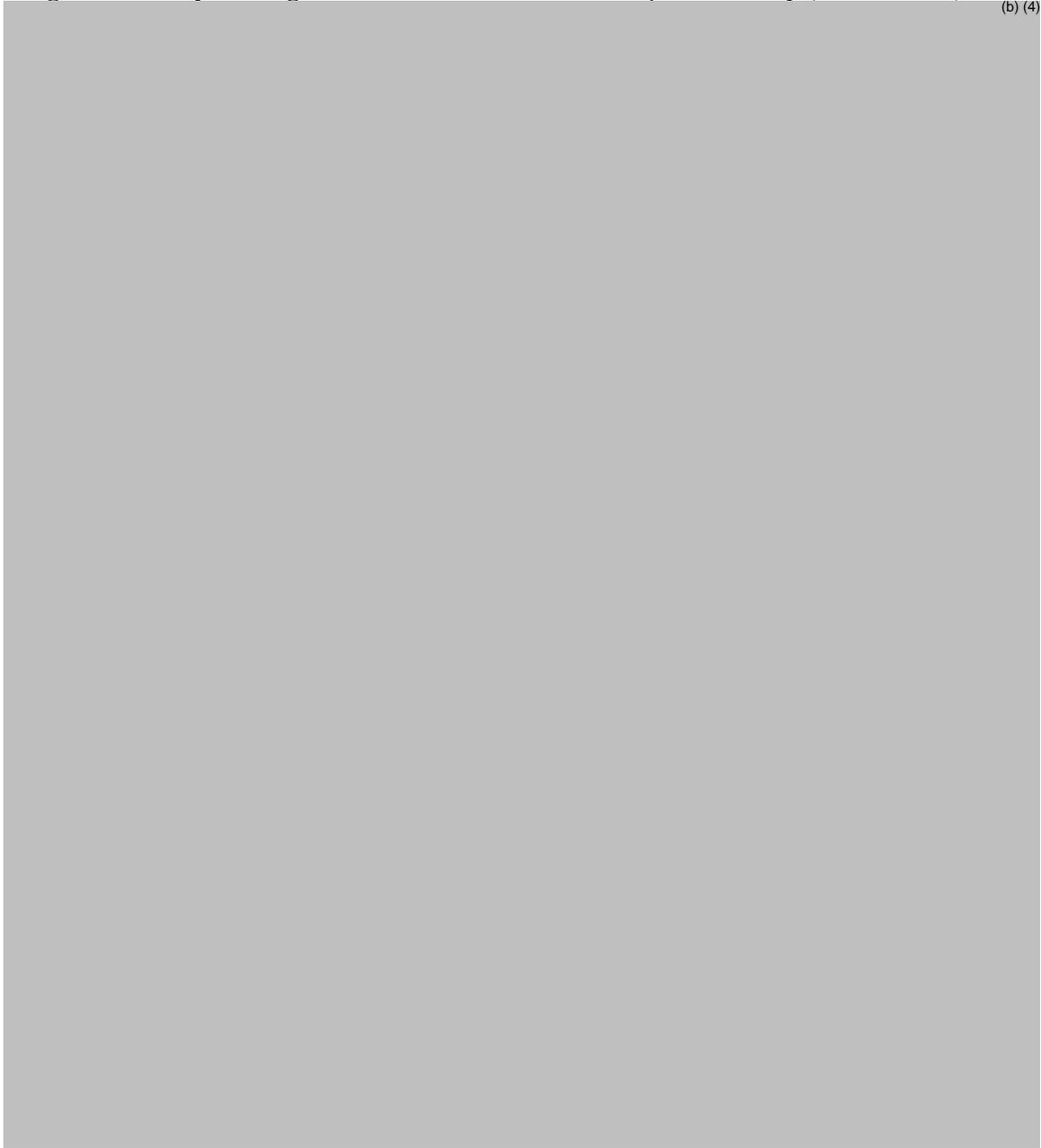
Table 9: Composition of Oxbryta Formulations (from M.2.7.1)

Components	Voxelotor PIC 50 mg, 100 mg		Voxelotor Capsules 300 mg	Voxelotor Capsules 300 mg	Voxelotor F1 Tablets 300 mg	Voxelotor F2 Tablets 300 mg	Voxelotor F2 Tablets 900 mg	Voxelotor F2 Tablets 500 mg
	Unit Weight (mg/capsule)				Unit Weight (mg/tablet)			
GBT440	50.0	100.0	—	—	—	—	—	—
GBT440	—		300.00	300.00	300.0	300.0	900.0	500.0
(b) (4)								
	—				(b) (4)			
Microcrystalline Cellulose	(b) (4)							
Croscarmellose Sodium	(b) (4)							
Sodium Lauryl Sulfate	(b) (4)							
Colloidal Silicon Dioxide	(b) (4)							
Magnesium Stearate	(b) (4)							
	—				Film Coating (Color Coat)			
(b) (4)								
Use	Investigational							Proposed commercial product for adults and (b) (4)

Abbreviations: (b) (4) F1, Formulation 1; F2, Formulation 2; PIC, Powder in Capsule.  
Source: Module 3.2.P.2.2.

Figure 18: Oxbryta Dosage Forms and Formulation Development History (from M.2.7.1)

(b) (4)



A comparison of (b) (4) and (b) (4) formulations is presented in Table 10 below, in which (b) (4). According to SUPAC-IR guidance, these changes are considered the Level 1 change.

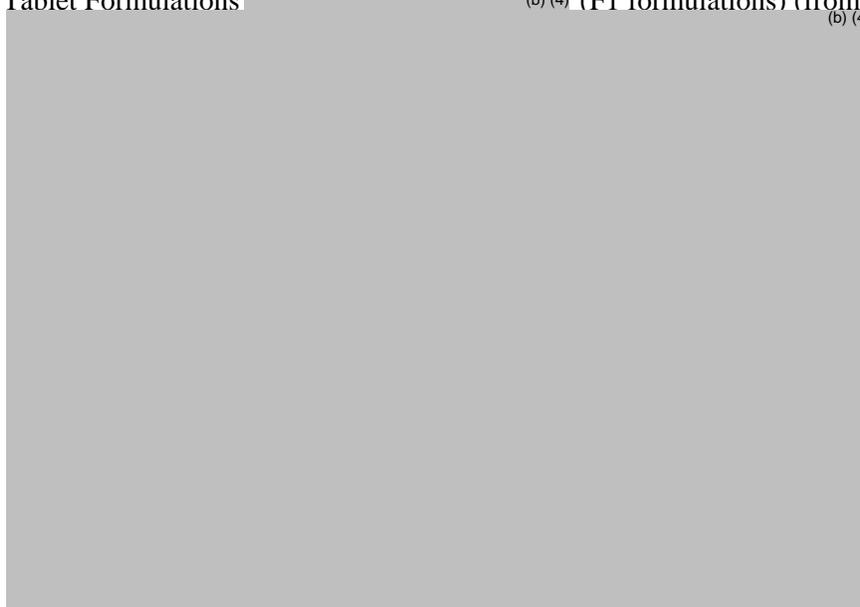
Table 10: Composition of Oxbryta (b) (4) Capsule Formulation (from M.3.2.P.2)

Ingredient	Function	Unit Weight (% w/w)	Unit Quantity (mg)	
Voxelotor	Active	(b) (4)	300	300
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Croscarmellose Sodium	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Magnesium Stearate	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Total	—	(b) (4)	(b) (4)	(b) (4)

MCC, microcrystalline cellulose.

When F1 formulation was developed, two formulations (b) (4) were studied (as presented in Table 11) below. The Applicant conducted a dog PK study (report in PRC-19-009-R) to demonstrate that both F2 formulations have comparable PK data with (b) (4) formulation, therefore, (b) (4), which was designated as Formulation 1 (F1).

Table 11: Tablet Formulations (b) (4) (F1 formulations) (from M.3.2.P.2)



A comparison of F1 and F2 formulations is presented in Table 12 below, (b) (4)



Table 12: Oxbryta Tablet Formulation 1 and Tablet Formulation 2 (from M.3.2.P.2)

Function in Formulation	Formulation 1		Formulation 2	
	Components	Quantity (%w/w)	Components	Quantity (%w/w)
Active Ingredient (b) (4)	Voxelotor	(b) (4)	Voxelotor	(b) (4)
	Microcrystalline cellulose	(b) (4)	Microcrystalline cellulose	(b) (4)
	Croscarmellose sodium	(b) (4)	Croscarmellose sodium	(b) (4)
	Sodium lauryl sulfate		Sodium lauryl sulfate	
	Magnesium stearate		Magnesium stearate	
	(b) (4) yellow coating		(b) (4) yellow coating	
<b>Dosage 300 mg</b>				
Core Tablet (mg)	(b) (4)			
Coated Tablet (mg)	(b) (4)			
<b>Dosage 900 mg</b>				
Core Tablet (mg)	(b) (4)			
Coated Tablet (mg)	(b) (4)			
<b>Dosage 500 mg</b>				
Core Tablet (mg)	(b) (4)			
Coated Tablet (mg)	(b) (4)			

For all F2 formulations, 300 mg tablets were used for Phase 1, Phase 3 and Phase 4 clinical studies. 900 mg tablets were used in a rBA study prior to registration campaign allowing bridging F2 tablet formulation to F1 tablet formulation. Also, 900 mg tablets were developed as the largest expected tablet size and dosage strength to support the registration stability bracketing strategy. 500 mg tablets are designed as the proposed commercial drug product.

The Applicant also conducted four in vivo relative bioavailability/bioequivalence (BA/BE) studies to establish the in vivo bridging among the development formulations, such as PIC, (b) (4) 1/2, and F1/2, listed in Table 13.

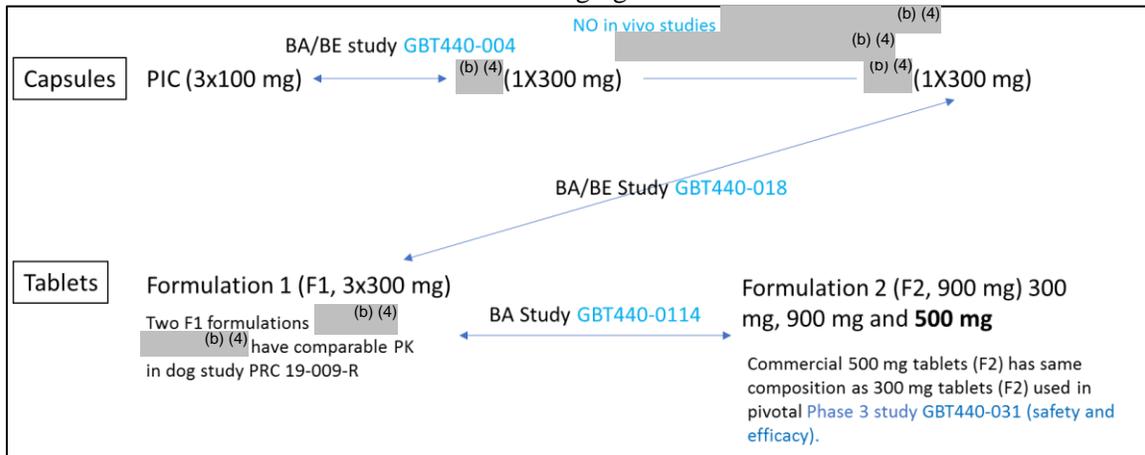
Table 13: Summary of Biopharmaceutics Clinical Studies (from M.2.7.1)

Type of Study	Study No.	Study Design	Voxelotor Dose Formulation, & Route of Administration	No. of Subjects	Study Population
Relative BA and PK	GBT440-004	Open-label, single-dose, crossover	Single oral dose of 300-mg (b) (4) capsule vs 3 × 100-mg PIC	26	Healthy subjects
Relative BA and PK	GBT440-018	Open-label, single-dose, crossover	Single oral dose of 300-mg F1 tablet vs 300-mg (b) (4) capsule	26	Healthy subjects
Relative BA and PK	GBT440-0114	Open-label, single-dose, crossover	Single oral dose of 900-mg F2 tablet vs 3 × 300-mg F1 tablet	20	Healthy subjects
Food effect	GBT440-005	Open-label, single-dose, crossover	Single oral dose of 900 mg (3 × 300-mg (b) (4) capsules) with a high-fat meal vs under fasted conditions	16	Healthy subjects

Abbreviations: BA, bioavailability; (b) (4) F1, Formulation 1; F2, Formulation 2; No., number; PIC, Powder in Capsule; PK, pharmacokinetic(s).

The above BA/BE studies will be reviewed by the Office of Clinical Pharmacology (OCP). This Reviewer summarized a schematic representation of the formulation development and the related in vivo bridging studies, as showed in Figure 19 below.

Figure 19: A schematic representation of the formulation development and the related in vivo bridging studies



The summarized BA/BE results are presented in Table 14 below:

Table 14: Summary of Relative Bioavailability of Test Formulations to Reference Formulations Across Studies (from M.2.7.1)

Study Number	Test Formulation	Reference Formulation	Geometric LS Mean Ratio (90% CI)		
			C <sub>max</sub> (µg/mL)	AUC <sub>t</sub> (µg • h/mL)	AUC <sub>∞</sub> (µg • h/mL)
GBT440-004	300-mg (b)(4) capsule	3 × 100-mg PIC	1.047 (0.965, 1.136)	0.993 (0.951, 1.036)	0.992 (0.950, 1.036)
GBT440-018	300-mg F1 tablet	300-mg (b)(4) capsule	1.013 (0.961, 1.068)	1.041 (0.986, 1.099)	1.040 (0.985, 1.098)
GBT440-0114	900-mg F2 tablet <sup>a</sup>	3 × 300-mg F1 tablet <sup>b</sup>	1.004 (0.863, 1.167)	1.032 (0.882, 1.208)	1.034 (0.885, 1.208)

Abbreviations: AUC<sub>t</sub>, area under the concentration-time curve from time zero to time of the last quantifiable concentration; AUC<sub>∞</sub>, area under the concentration-time curve from time zero extrapolated to infinity; (b)(4) C<sub>max</sub>, maximum observed concentration; CI, confidence interval; F1, Formulation 1; F2, Formulation 2; LS, least-squares; PIC, Powder in Capsule; PK, pharmacokinetic(s).

Notes: The log-transformed PK parameters (C<sub>max</sub>, AUC<sub>t</sub>, and AUC<sub>∞</sub>) were analyzed using a linear mixed model, with fixed effects for sequence, treatment, period, and subject nested within sequence as random effect.

<sup>a</sup> Tablet formulation with (b)(4)  
<sup>b</sup> Tablet formulation without (b)(4)

Source: GBT440-004 CSR Table 14.2.3.1, GBT440-018 CSR Table 14.2.3.1, and GBT440-0114 CSR Table 14.2.3.1.

As the data presented in Table 14, on face, the *in vivo* bridging among different formulations (e.g., PIC, (b)(4) 1/2, and F1/2) during pharmaceutical development have been established. Additionally, the F2 300 mg tablets were developed to enable manufacturing process improvement and to support potentially higher clinical doses in later-phase clinical studies, including the pivotal Phase 3 efficacy and safety study GBT440-031 in

adults and adolescents with SCD. The commercial formulation (F2 5 mg tablets) is compositionally proportional compared to the F2 300 mg tablets. Therefore, from the Biopharmaceutics perspective, the bridge between the clinical formulations and the commercial formulation is established, so that no additional *in vitro* or *in vivo* bridging studies are needed.

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### NDA 213137 Initial Risk Assessment Table

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	FAILURE MODE	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN
Assay, Stability	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	(b) (4)	4	2	Release (1)	8
					Stability (3)	24
Physical stability (solid state)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>		Crystalline (3)	3	4	36
Content Uniformity	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>		High Loading Dose (3)	3	4	16
Microbial Limits	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>		1	2	5	10
Dissolution – BCS Class II & IV	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw Materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>		4	2	4	32



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