

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**212728Orig1s000**

**PRODUCT QUALITY REVIEW(S)**

## RECOMMENDATION: Approval

### NDA 212728 Review 1

<b>Drug Product Name</b>	TRADENAME (rimegepant)
<b>Dosage Form</b>	Orally disintegrating tablet
<b>Strength</b>	75 mg
<b>Route of Administration</b>	Oral
<b>Rx/OTC Dispensed</b>	Rx
<b>Applicant</b>	Biohaven Pharmaceutical Holding Ltd
<b>US agent, if applicable</b>	Biohaven Pharmaceuticals Inc.

#### QUALITY TEAM

<b>Discipline</b>	<b>Primary Assessment</b>	<b>Secondary Assessment</b>
Drug Substance	Rajan Pragani	Suong (Su) Tran
Drug Product/Labeling	Stephanie Emory	Julia Pinto
Manufacturing	Tianhong Tim Zhou	Erin Kim
Microbiology	N/A	N/A
Biopharmaceutics	Qi Zhang	Ta-Chen Wu
Regulatory Business Process Manager	Dahlia Walters	
Application Technical Lead	Martha Heimann	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

<b>Submission(s) Reviewed</b>	<b>Document Date</b>	<b>Discipline(s) Affected</b>
SD-4, Original NDA <sup>1</sup>	6/27/2019	All
SD-12, Labeling/PI	9/13/2019	Labeling
SD-16, Response to IR	10/11/2019	Drug product, manufacturing, biopharmaceutics
SD-18, Response to IR <sup>2</sup>	10/18/2019	Biopharmaceutics
SD-20, Response to IR	11/1/2019	Drug product
SD-22, Response to IR	11/15/2019	Manufacturing, biopharmaceutics
SD-25, Response to IR	11/25/2019	Drug product
SD-30, Response to IR	12/5/2019	Biopharmaceutics
SD-32, Response to IR	12/10/2019	Biopharmaceutics
SD-33, Response to IR	12/13/2019	Drug product
SD-35, Response to IR	12/19/2019	Biopharmaceutics
SD-37, Labeling/Container	12/30/2019	Labeling

<sup>1</sup> NDA (b) (4) (rimegepant tablets), submitted 6/28/2019, is cross-referenced for drug substance and facility information.

<sup>2</sup> Cross-reference to NDA 21270, SD-18, submitted 10/18/2019

# QUALITY ASSESSMENT DATA SHEET

## 1. RELATED/SUPPORTING DOCUMENTS

### A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessed	Comments
(b) (4)	III	(b) (4)	(b) (4)	N/A	N/A	Adequate information in NDA.

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

Document	Application Number	Description
IND	109886	Development of rimegepant for treatment of migraine
NDA	212728	Concurrent NDA submitted for rimegepant tablets, which is cross-referenced for drug substance and facility information

## 2. CONSULTS

None

# EXECUTIVE SUMMARY

## I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The OPQ review team recommends **Approval** of NDA 212728 for TRADENAME (rimegepant) orally disintegrating tablets. The application, as amended in response to Agency information requests (IRs), provides adequate information to ensure that the applicant can consistently manufacture a product that is suitable for use by the intended patients.

## II. SUMMARY OF QUALITY ASSESSMENTS

### A. Product Overview

The Applicant, Biohaven, has developed rimegepant, a new molecular entity that is an orally active, small molecule calcitonin gene-related peptide (CGRP) receptor antagonist, for acute treatment of migraine. Two dosage forms, each containing 75 mg rimegepant are proposed. NDA 212728 provides for an orally disintegrating tablet (ODT) formulation. NDA (b) (4) submitted concurrently, provides for conventional immediate-release tablets.

Rimegepant ODT is designed to disintegrate rapidly in contact with saliva when placed on the tongue. The active ingredient is released as particles that are transported by natural salivary drainage and swallowing of saliva to the gastrointestinal tract, where it dissolves and is absorbed. The product is using proprietary “Zydis” technology in which individual tablets are produced by lyophilizing an aqueous solution or suspension containing the active ingredient and excipients in a preformed blister. Critical quality attributes for Zydis-type ODTs include drug substance particle size, homogeneity of the bulk solution or suspension during filling of the blisters, physical integrity of the tablets, disintegration time, chemical stability, and protection from moisture. The initial risk assessment identified dissolution and palatability as moderate risk attributes for the product.

<b>Proposed indication(s) including intended patient population</b>	Treatment of acute migraine.
<b>Duration of treatment</b>	Chronic intermittent
<b>Maximum daily dose</b>	75 mg
<b>Alternative methods of administration</b>	The ODT may be placed under the tongue.

## B. Quality Assessment Overview

**Drug Substance: Adequate**

*Note: Manufacturing and control information for the active ingredient, rimegepant sulfate, is incorporated by cross-reference to the Applicant's pending NDA (b) (4) and the drug substance review is filed under that application. Key points from the review are summarized below.*

The drug substance, rimegepant sulfate, is manufactured by two contract manufacturers under the Applicant's control. Batches from both manufacturers were found to be comparable. The drug substance structure is adequately characterized, with stereochemistry confirmed by single crystal x-ray crystallography. The manufacturing process is adequately described, and designated starting materials are consistent with ICH Q11 recommendations. The commercial manufacturing process produces a single solid-state form, which is controlled in the drug substance specification. Two specified impurities with proposed limits above the ICH Q3A qualification threshold were adequately qualified and no mutagenic impurity risks were identified. Adequate justification was provided for tests and acceptance criteria included in the specification, and for omission of specific tests. Based on the stability data provided, the proposed (b) (4) retest date for drug substance stored at (b) (4) is acceptable.

**Drug Product: Adequate**

The rimegepant ODT is a lyophilized tablet that contains 85.65 mg of the drug substance, rimegepant sulfate, equivalent to 75 mg of rimegepant base. The formulation includes gelatin and mannitol (b) (4) sucralose (b) (4) (b) (4). The drug substance is present in the tablet as discrete particles with a single polymorphic form. The product is manufactured by Catalent and the Applicant on Catalent's experience manufacturing similar ODT products to inform choice of excipients and formulation development.

The proposed regulatory specification includes recommended universal tests (e.g., appearance, identity, assay/impurities, etc.) and tests, such as disintegration time, recommended for the dosage form. The proposed acceptance criteria for all test parameters are adequately justified by the Applicant. Analytical procedures are well-described and validated appropriately.

Rimegepant ODTs will be packaged in laminated aluminum blisters (b) (4) (b) (4). Based on the long-term and accelerated stability data provided, the proposed **24-month shelf-life for product stored at controlled room temperature is granted.**

*Manufacturing:*                    **Adequate**

Per prior agreement with the Agency, (b) (4) is designated as the first step in the drug product manufacturing process. Drug substance particle size is considered critical (b) (4)

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

The proposed commercial batch size is (b) (4), a 3x scale-up from the largest registration batch. The Applicant has provided adequate justification for changes to equipment, process parameters, and processing times to support commercial production.

All facilities involved in the manufacture and testing of rimegepant sulfate and Rimegepant Orally Disintegrating Tablets are currently acceptable.

*Biopharmaceutics:*                    **Adequate**

The proposed Rimegepant ODT product is a freeze-dried formulation with very fast disintegration (NMT (b) (4) seconds) and rapid dissolution at pH 1.2, pH 4.5, and pH 6.8. The ODT formulation is considered bioequivalent to the Rimegepant Tablet, with a similar Tmax (1.5 vs. 1.9 hours). The adequacy of the proposed dissolution method ((b) (4) mL of 50 mM sodium acetate buffer at pH 4.5 and 37°C, using USP Apparatus 2 at 50 rpm) and acceptance criterion (NLT (b) (4)% (Q) at 15 minutes) was evaluated. Based on the data provided, the Applicant was asked to reduce the volume of the dissolution medium from (b) (4) mL to 500 mL. The Applicant agreed and will revise the dissolution method in a CBE Supplement post-NDA action date. The final dissolution test, with a volume of 500 mL dissolution medium, is deemed acceptable for batch release and stability testing.

The proposed commercial ODT product has the same formulation and manufacturing site as for the product batches used in bioequivalence studies, food effect study, and the Phase 3 efficacy study. Thus, bridging between the clinical formulation and commercial product is not needed.

*Labeling:*                                    **Adequate**

The proposed labeling, as revised per review recommendations, is deemed adequate from a quality perspective

*Environmental:*                    **Adequate**

The applicant submitted a claim for categorical exclusion under 21 CFR §25.31(b). Approval of the application would increase use of rimegepant. However, the expected environmental introduction concentration (EIC) is less than 1 part per billion and there are no extraordinary circumstances. **The claim for categorical exclusion is granted.**

*Methods Verification:*

Verification of analytical procedures submitted in the NDA by FDA laboratories was not requested during the review.

### C. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Comments
Assay, stability	Formulation, container closure, moisture, process parameters	L	(b) (4)	Adequate	
Content uniformity (CU)	Formulation, raw materials, process parameters, scale/equipment/site	L		Adequate	
Physical stability (solid state)	Formulation, raw materials, process parameters, scale/equipment/site	L		Adequate	
Microbial limits	Formulation, raw materials, process parameters, moisture, container closure	L		Adequate	
Disintegration	Formulation, raw materials, process parameters, scale/equipment/site	L		Adequate	
Dissolution	Formulation, raw materials, process parameters, scale/equipment/site	L		Adequate	
Palatability	Formulation, raw materials, container closure	M		Adequate	Commercial formulation is the same as the formulation used in clinical trials and bioequivalence studies.

**D. List of Deficiencies for Complete Response: Not applicable.**

*Application Technical Lead Name and Date: Martha R. Heimann, 1/22/2020*

APPEARS THIS WAY ON ORIGINAL



Martha  
Heimann

Digitally signed by Martha Heimann

Date: 1/22/2020 01:35:18PM

GUID: 504f845f00000ed260627d268a8cdc9d

21 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

## CHAPTER IV: LABELING

### 1.0 PRESCRIBING INFORMATION

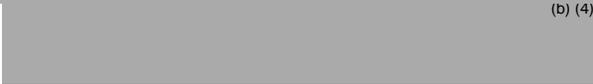
#### Assessment of Product Quality Related Aspects of the Prescribing Information:

#### 1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
<b>Product Title in Highlights</b>		
Proprietary name	TRADENAME™-ODT	Adequate
Established name(s)	(rimegepant) orally disintegrating	Adequate
Route(s) of administration	tablets, for sublingual or oral use (b) (4)	Adequate
<b>Dosage Forms and Strengths Heading in Highlights</b>		
Summary of the dosage form(s) and strength(s) in metric system.	<ul style="list-style-type: none"> <li>TRADENAME-ODT Orally Disintegrating Tablets: 75 mg (b) (4)</li> </ul>	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
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.	N/A	N/A

**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)	Instruct the patient on the following administration instructions: <ul style="list-style-type: none"> <li>• Use dry hands when opening the blister pack.</li> <li>• Peel back the foil covering of one blister and gently remove the ODT. Do not push the ODT through the foil.</li> <li>•  (b) (4)</li> <li>•  (b) (4)</li> <li>• Take the ODT immediately after opening the blister pack. Do not store the ODT outside the blister pack for future use.</li> </ul>	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)	(b) (4)	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting		Remove (b) (4) as it may be considered as promotional and relates to the manufacturing process, not the finished product appearance.
Strength(s) in metric system	75 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	(b) (4)	State the strength based on the free base: "...contains 75 mg rimegepant." The equivalency statement is provided in Section 11.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
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.	N/A	N/A

### 1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
<b>DESCRIPTION section</b>		
Proprietary and established name(s)	(b) (4)	Adequate
Dosage form(s) and route(s) of administration		Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.		Include the quantity of rimegepant sulfate in the equivalency statement: "...contains 85.65 mg rimegepant sulfate, equivalent to 75 mg rimegepant free base."
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.		List the individual components of the (b) (4)
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.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/therapeutic class	TRADENAME-ODT (b) (4) contains rimegepant sulfate, a calcitonin gene-related peptide receptor antagonist.	Adequate

**Section 11 (DESCRIPTION) Continued**

Item	Information Provided in the NDA	Assessor's Comments
Chemical name, structural formula, molecular weight	Rimegepant sulfate is described chemically as (5S,6S,9R)-5-amino-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)-1-piperidinecarboxylate hemisulfate sesquihydrate and its structural formula is [structure provided]. Its empirical formula is C <sub>28</sub> H <sub>28</sub> F <sub>2</sub> N <sub>6</sub> O <sub>3</sub> · 0.5 H <sub>2</sub> SO <sub>4</sub> · 1.5 H <sub>2</sub> O, representing a molecular weight of 610.63. Rimegepant free base has a molecular weight of 534.56.	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	Rimegepant sulfate is a white to off-white, crystalline solid that is slightly soluble in water.	Adequate
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	N/A

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

Item	Information Provided in the NDA	Assessor's Comments
<b>HOW SUPPLIED/STORAGE AND HANDLING section</b>		
Available dosage form(s) Strength(s) in metric system	<p>TRADNAME-ODT 75 mg orally disintegrating tablets are white to off-white, circular, (b) (4) debossed with (b) (4) symbol (b) (4), supplied in cartons containing a blister pack of 8 orally disintegrating tablets. Each ODT contains 75 mg rimegepant (b) (4)</p>	<p>Adequate</p> <p>(b) (4)</p> <p>State the strength based on the free base: "...contains 75 mg rimegepant."</p> <p>(b) (4)</p>
Available units (e.g., bottles of 100 tablets)	NDC: 72618-3000-2	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4)	<p>Remove (b) (4)</p> <p>(b) (4), as it may be considered as promotional and relates to the manufacturing process, not the finished product appearance.</p>
Include information about child-resistant packaging	None	(b) (4)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
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.	N/A	N/A

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

Item	Information Provided in the NDA	Assessor's Comments
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
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.	N/A	N/A
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	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	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store TRADENAME-ODT (b) (4) at controlled room temperature, 20°C to 25°C (68°F to 77°F); with excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature].	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."	N/A	N/A

### 1.2.5 Other Sections of Labeling – N/A

### 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 (b) (4) Biohaven Pharmaceuticals, Inc. New Haven, CT 06510 USA	Adequate

## 2.0 PATIENT INFORMATION section

### How should I take TRADENAME-ODT (b) (4) ?

- To take TRADENAME-ODT orally disintegrating tablets (ODT):
  - Use dry hands when opening the blister pack.
  - Peel back the foil covering of one blister and gently remove the ODT. **Do not** push the ODT through the foil.
  - (b) (4)
  - (b) (4)
  - Take the ODT immediately after opening the blister pack. Do not store the ODT outside the blister pack for future use.

### How should I store TRADENAME-ODT (b) (4) ?

- Store TRADENAME-ODT in the blister package that it comes in.
- Store TRADENAME-ODT (b) (4) at room temperature between 68°F to 77°F (20°C to 25°C). (b) (4)

Keep TRADENAME-ODT, (b) (4) and all medicines out of the reach of children.

### What are the ingredients in TRADENAME-ODT (b) (4) ?

Active ingredient in TRADENAME-ODT (b) (4): rimegepant

Inactive ingredients in TRADENAME-ODT: gelatin, mannitol, sucralose, (b) (4)

### Assessment of Product Quality Related Aspects of Patient Information section:

**Adequate, pending the listing of the individual components of the (b) (4)**

Item	Information Provided in the NDA	Assessor's Comments about Blister/Carton/Bottle Labeling
Proprietary name, established name, and dosage form (font size and prominence)	See representative labels above	Adequate
Dosage strength		Adequate
Route of administration		Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	missing	Due to size constraints, the equivalency statement may be omitted from the blister labels. However, it should be included on the ODT carton and tablet bottle labels.
Net contents (e.g. tablet count)	See representative labels above	Adequate
"Rx only" displayed on the principal display		Adequate
NDC number		Adequate
Lot number and expiration date		Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.		Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	N/A
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Bar code	See representative labels above	Adequate

Item	Information Provided in the NDA	Assessor's Comments about ODT Blister/Carton Labeling
Name of manufacturer/distributor	See representative label above	Adequate
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap overseal	N/A	N/A
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.	N/A	N/A
And others, if space is available	N/A	N/A

**Assessment of Carton and Container Labeling: Adequate, pending addition of equivalency statement**

## ITEMS FOR ADDITIONAL ASSESSMENT

Throughout the PI, except in section 11, state the strength based on rimegepant (free base), (b) (4). In Section 11 Description, the equivalency statement should appear, including the quantities of both the salt and free base.

Throughout the PI, remove (b) (4) as it may be considered as promotional and relates to the manufacturing process, not the finished product appearance.

In PI Sections 11 and Patient Information, list the individual components of the (b) (4)

In the ODT carton labels and (b) (4), add the equivalency statement, including the quantities of both the salt and free base.

## Overall Assessment and Recommendation:

**Adequate, pending the revisions listed above.**



Stephanie  
Emory

Digitally signed by Stephanie Emory  
Date: 12/09/2019 11:41:57AM  
GUID: 56eb17470045bc2d4c3c9462af6ca8e3



Julia  
Pinto

Digitally signed by Julia Pinto  
Date: 12/11/2019 11:35:43AM  
GUID: 5050dbcb00001294a888a4bdc20a3a58

39 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

## CHAPTER VI: BIOPHARMACEUTICS

<b>NDA Number</b>	212728 (Priority Review); 505(b)(1)-NME
<b>Assessment Cycle Number</b>	1
<b>Drug Product Name/ Strength</b>	(b) (4)-ODT (rimegepant) orally disintegrating tablets, for sublingual or oral use, 75 mg
<b>Dosage Form</b>	Orally Disintegrating Tablet (ODT)
<b>Administration</b>	Oral (75 mg orally, (b) (4))
<b>Applicant Name</b>	Biohaven Pharmaceuticals
<b>Therapeutic Classification/ OND Division</b>	Psychiatry/CDER/ON/DP
<b>Proposed Indication</b>	(b) (4) ODT is a calcitonin gene-related peptide receptor antagonist indicated for the acute treatment of migraine in adults.
<b>Primary Reviewer</b>	Qi Zhang, Ph.D.
<b>Secondary Reviewer</b>	Ta-Chen Wu, Ph.D.

### REVIEW SUMMARY

This Biopharmaceutics review focused on evaluation of the adequacy of the proposed dissolution method and acceptance criterion. The Applicant agreed and will revise the dissolution method to lower the dissolution medium volume from (b) (4) mL to 500 mL in a CBE Supplement post-NDA action date, as per the FDA’s recommendation during the review cycle. The final dissolution test with a volume of 500 mL dissolution medium, as summarized below, for batch release and stability testing for the proposed ODT product is deemed acceptable, based on the totality of information/data provided [e.g., controls of API particle size and polymorphic form, freeze dried formulation with very fast disintegration (NMT (b) (4) seconds), very rapid dissolution across pH 1.2, pH 4.5 and pH 6.8, bioequivalence (BE) and similar Tmax (1.5 vs. 1.9 hours) to the (b) (4) Tablets].

The FDA approved dissolution method and acceptance criterion are as follows:

USP Apparatus	Speed (RPM)	Medium	Volume/Temp	Acceptance Criterion
II	50	50 mM sodium acetate buffer, pH 4.5	500 mL/37°C	NLT (b) (4)% (Q) at 15 minutes

It is noted that product bridging is not needed because the proposed commercial ODT product has the same formulation and manufacturing site as those of the product batches used in the BE studies, food effect study, and Phase 3 efficacy study.

### RECOMMENDATION:

From the Biopharmaceutics perspective, NDA 212728 for (b) (4)-ODT (rimegepant) orally disintegrating tablets, 75 mg, is recommended for APPROVAL.

**Labelling Recommendation:**

*The ODT may not dissolve completely in the mouth (under the tongue) before being swallowed because of the API's low aqueous solubility. Accordingly, Division of Biopharmaceutics recommends replacing (b) (4) with “will quickly disintegrate to be dissolved” for the proposed labelling.*

**BIOPHARMACEUTICS ASSESSMENT**

**LIST of SUBMISSIONS BEING REVIEWED**

eCTD # (SND #)	Received date	Document
0001(1)	06/28/2019	Original Submission
0017(18)	10/18/2019	Response to Quality Information Request
0021(22)	11/15/2019	Response to Quality Information Request
0028(30)	12/05/2019	Response to Quality Information Request
0030(32)	12/10/2019	Response to Quality Information Request
	12/16/2019	Response via Email to Quality Information Request
0033(35)	12/19/2019	Response to Quality Information Request

**BIOPHARMACEUTICS GENERAL INFORMATION**

***Drug Substance [Rimegepant Sulfate (Hemisulfate Sesquihydrate) (BHV-3000)]***

<b>pKa/Log D<sub>7.4</sub></b>	2.1, 6.5, 9.8 (weak base)/1.74
<b>Particle Size</b>	<i>d (0.1): NMT (b) (4) μm; d (0.5): NMT (b) (4) μm; d (0.9): NMT (b) (4) μm. (Noted that the CMC information for the drug substance are provided under NDA (b) (4) for (b) (4) (rimegepant) Tablet. The Applicant tightened the PSD acceptance criteria in response to the Biopharm IR of Oct 4th, 2019 under NDA (b) (4) The API is (b) (4) during the ODT manufacturing. (b) (4) specification for the (b) (4) (b) (4)</i>
<b>Polymorphism</b>	<i>Only one crystalline form (b) (4) identified by XRD. No other polymorphs have been observed in GMP batches and stability batches per the Applicant.</i>
<b>Solubility</b>	<i>Low and pH-dependent solubility per BCS criteria [8.575 mg/mL to 1.353 mg/mL from pH 1.4 to pH 5.6, and 0.0973 mg/mL to 0.0629 mg/mL from pH 6.8 to pH 7.6 vs. 0.3 mg/mL in 250 mL for the 75 mg strength dose]. The solubility data for the API were generated using (b) (4) drug substance. Per the Applicant, the solubility of the (b) (4) API is expected to be similar to that of (b) (4) API since the difference in API total surface area/particle size does not affect solubility. Only the intrinsic dissolution could be potentially affected based on surface area/particle size.</i>  <i>Giving the solubility data at 22°C across the physiological range from pH 1 to pH 7.6, the amount of the drug substance in the ODT is not expected to be dissolved in the mouth (under the tongue) before the swallowing in approximately 1 mL saliva for the 75 mg dose. Note that saliva has a pH normal range of 6.2-7.6 (pH 7.4 reported for healthy subjects).</i>
<b>Permeability</b>	Not reported by the Applicant.
<b>BCS Class</b>	Not reported by the Applicant.

<b>BCS Class Designation</b>	Not submitted nor required.
------------------------------	-----------------------------

**Drug Product**

The proposed ODT is a freeze dried orally administered formulation and is designed to rapidly disintegrate in the mouth. It is manufactured with (b) (4) API using Zydis® (lyophilized) process by Catalent, Inc., for Biohaven. The drug product formulation contains gelatin and mannitol as (b) (4), and sucralose (b) (4).

**Pharmacokinetics**

<b>Tmax</b>	1.5 (ODT) vs 1.9 (Tablet)
<b>Absolute BA</b>	Approximately 64% (fasted)
<b>BE</b>	The ODT administered sublingually or on the tongue is BE to the Tablets.
<b>Food Effect</b>	A high-fat meal decreased the mean AUC and Cmax of both ODT and Tablets by 30% to 38% and 33% to 53%, respectively, and delayed the Tmax by approximately one hour. The ODT and the Tablets may be administered without regard to meals. (b) (4).

**DISSOLUTION**

**Dissolution Method and Acceptance Criterion**

USP Apparatus	Speed (RPM)	Medium	Volume/Temp	Acceptance Criterion
II	50	50 mM sodium acetate buffer, pH 4.5	Proposed: (b) (4) mL/37°C <b>Recommended:</b> <b>500 mL/37°C</b>	NLT (b) (4)% (Q) at 15 minutes

The currently proposed dissolution method (Method AM848) for the proposed (b) (4) ODT is a modification of that described for (b) (4) (Rimegepant) Tablet 75 mg [*USP apparatus II (paddle) at (b) (4) rpm in (b) (4) mL 50 mM sodium acetate buffer pH 4.5; refer to Biopharmaceutics Review for NDA (b) (4) for the adequacy of the method*]. The modified method employs a lower rotation speed of 50 rpm and a higher volume of (b) (4) mL dissolution medium.

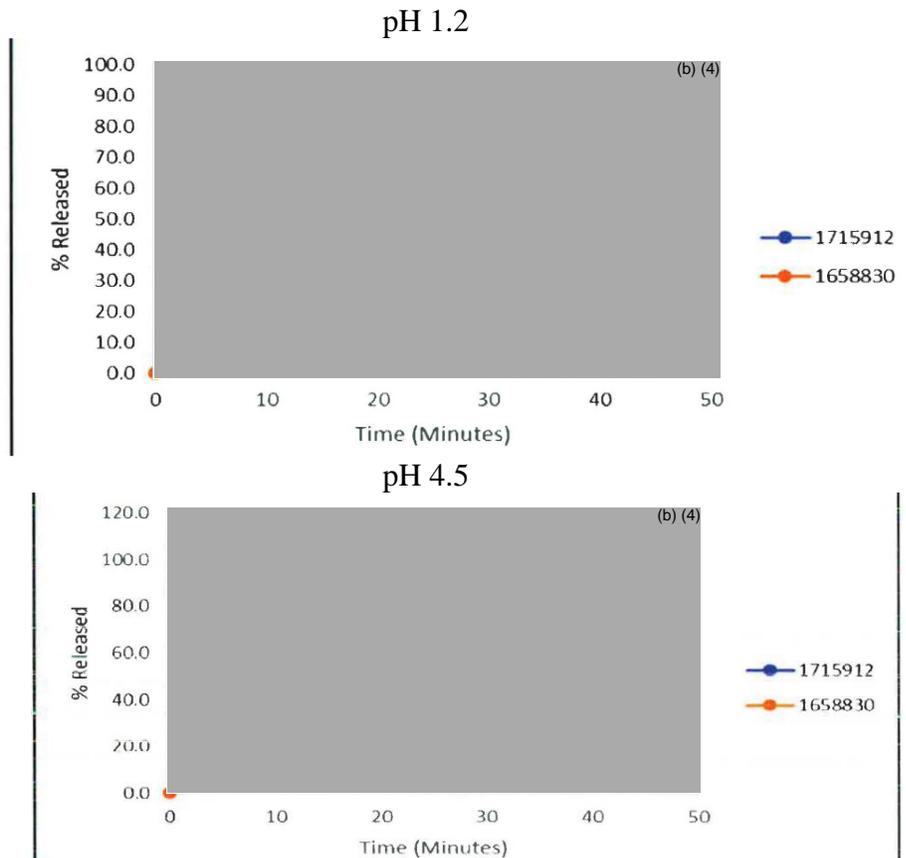
During the review cycle, the Applicant was requested to provide justification for the selection of (b) (4) mL dissolution medium volume. The Applicant responded that the solubility of BHV-3000 at pH 4.5 acetate buffer is approximately 2.1 mg/mL, (b) (4). The Applicant’s response is not acceptable. Based on the FDA’s current practice, the lowest dissolution volume in which sink conditions are achieved should be used for the dissolution test. On December 10, 2019, the Applicant agreed to FDA’s request (Information Request dated 12/06/2019)

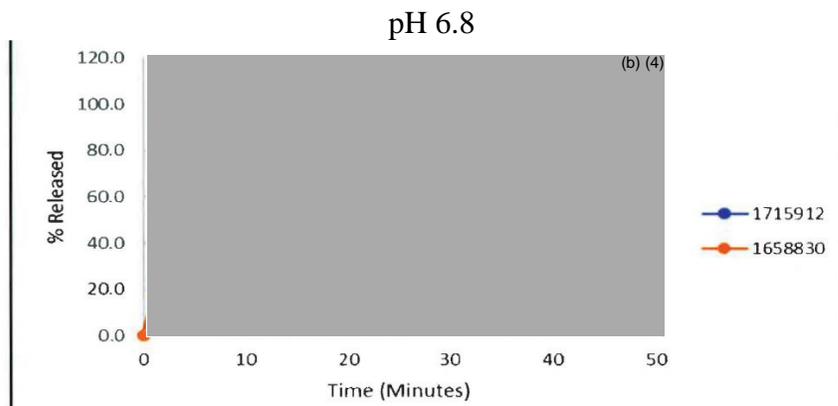
to lower the dissolution volume to 500 mL for the proposed ODT and will submit the supporting dissolution profile data post-NDA’s action date for the registration-stability batches and new manufactured commercial batches using both 500 mL and (b) (4) mL. The updated 3.2.P.5.2 and 3.2.P.5.3 will be presented as a CBE Supplement post-NDA action date as agreed upon by the FDA via email communication on December 16, 2019. The 500 mL dissolution method (Method TM7026) will be adopted post-NDA approval as the official commercial release and stability dissolution method immediately upon method validation and the resulting CBE Supplement filing.

The Biopharmaceutics review team determined that the dissolution method using 500 mL dissolution medium at a mild agitation speed of 50 rpm with the acceptance criterion of “Q=(b) (4)% in 15 minutes” is suitable for the proposed ODT product, based on the following information provided by the Applicant:

1. The dissolution is very rapid and complete (> (b) (4)% dissolution) across pH 1.2, pH 4.5, and pH 6.8 (**Figure 1**). The dissolution profiles in pH 4.5 and pH 6.8 media appear slower in the 3 and 6 minutes timepoints with > (b) (4)% release being consistently obtained at (b) (4) minutes using the (b) (4) mL dissolution method.

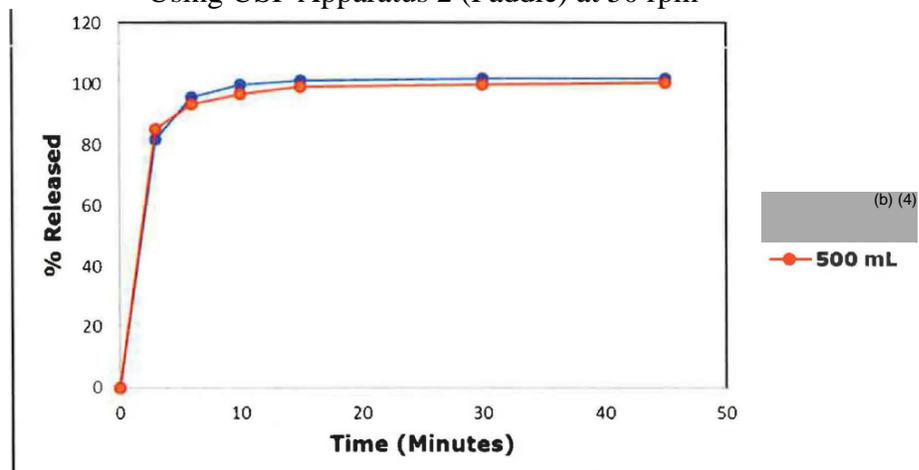
**Figure 1:** Dissolution Profiles of Registration Batch 1715912 Vs. Clinical Batch 1658830 at pH 1.2, pH 4.5 and pH 6.8 in (b) (4) mL Using USP Apparatus 2 (Paddle) at 50 rpm





- Based on the solubility data provided for the (b) (4) API, sink conditions are expected to be achieved in the lower 500 mL volume for the (b) (4) API. In addition, comparison of the dissolution profiles obtained for the clinical batch (1658830, **Figure 2**) and the other two registration batches confirmed that there is no difference between the profiles obtained using 500 mL and (b) (4) mL volumes.

**Figure 2:** Comparative Dissolution of Clinical Batch 1658830 in 500 mL and (b) (4) mL pH 4.5 Sodium Acetate Dissolution Medium Using USP Apparatus 2 (Paddle) at 50 rpm



- Due to the lyophilized formulation and associated manufacturing process, dissolution discrimination ability of the proposed ODT drug product with respect to the typical manufacturing parameters, such as tablet hardness, compression force, and disintegrant amounts is precluded and, therefore, is deemed not required.
- Critical material attributes (CMA) that could impact the solubility/dissolution are drug substance polymorphic form and particle size. The Applicant showed that crystalline form of the drug substance is thermodynamically stable and, additionally, (b) (4) and final particle size are tightly controlled during the drug product manufacture (refer to the Drug Product and the Process Reviews).

5. The ODT administered sublingually or on the tongue before being swallowed was shown BE to the oral tablets (LD), with similar Tmax values [refer to Studies BHV-3000-110 (Tablet vs. sublingual ODT), BHV3000-112 (Food Effect Tablet vs. sublingual ODT) and BHV3000-113 (Tablet vs. ODT on top of tongue and Food Effect ODT)] (refer to the Clinical Pharmacology Review for the adequacy of the BE studies), suggesting insignificant effect of ODT dissolution in the mouth on drug absorption compared to oral tablets.

## **BRIDGING THROUGHOUT PRODUCT DEVELOPMENT**

Bridging is not needed because the drug product formulation and manufacturing site of both registration/stability batches and proposed commercial product are the same as the clinical/stability batch 1658830 used in the BE studies BHV-3000-110 and BHV3000-113, Food Effect study BHV3000-112 and Phase 3 efficacy study BHV3000-303.



Qi  
Zhang

Digitally signed by Qi Zhang  
Date: 12/31/2019 08:30:54PM  
GUID: 547e17800007695c91eb10380b07939



Ta-Chen  
Wu

Digitally signed by Ta-Chen Wu  
Date: 12/31/2019 08:34:30PM  
GUID: 508da6df000269e151ff37cd8f4e13a1

-----  
**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/  
-----

DAHLIA A WALTERS  
01/22/2020 02:23:13 PM