

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212728Orig1s000

OTHER REVIEW(S)



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date: February 18, 2020

Reviewer/Team Leader: Catherine Callahan, PhD, MA
Division of Epidemiology I

Deputy Division Director: CAPT Sukhminder K. Sandhu, PhD, MPH, MS
Division of Epidemiology I

Subject: ARIA Sufficiency Memo for Pregnancy Safety Concerns

Drug Name: NURTEC (rimegepant)

Application Type/Number: NDAs (b) (4) & 212728

Sponsor: Biohaven Pharmaceuticals

OSE RCM #: 2019-1379



1. BACKGROUND INFORMATION

1.1. Medical Product

Rimegepant is a small molecule calcitonin gene-related peptide receptor antagonist (new molecular entity) indicated for the acute treatment of migraine in adults. The recommended dose is 75mg taken orally as needed. Rimegepant is administered orally or sublingually. The most common adverse reaction in clinical trials was nausea (1.5% in treatment group vs. 0.8% in placebo).

1.2. Describe the Safety Concern

The Division of Neurology 2 (DN2) requested that the Division of Epidemiology (DEPI) assess the sufficiency of ARIA for broad-based signal detection studies of rimegepant during pregnancy.

Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.¹

Embryo-fetal development studies were conducted in the rat and rabbit. Rimegepant was administered by oral gavage to pregnant rats at doses of 10, 60, or 300 mg/kg/day and rabbits at doses of 10, 25, or 50 mg/kg/day, during the period of organogenesis. At 300 mg/kg/day maternal toxicity coupled with decreased fetal weights, and minor delays in ossification were observed. No effects were seen at 60 mg/kg/day. In rabbits, no effects on embryo-fetal development were observed at 50 mg/kg/day (10-fold the maximum recommended human dose (MRHD)). In the prenatal and postnatal development study in rats administered rimegepant at doses of 10, 25, or 60 mg/kg/day, there were no compound-related effects on any parameters at any dose at exposures that were up to approximately 38-fold the MRHD on Gestation Day 6.

There are no adequate and well-controlled studies that investigated adverse pregnancy outcomes after rimegepant exposure and a lack of pregnancy studies generally. Rimegepant had a mean elimination half-life of 6.15 and 4.81 hours for 4 x 75 mg and 1 x 75 mg regimen, respectively². In the rimegepant clinical studies, there were 24 pregnancies reported after at least one dose of rimegepant, 3 resulted in live full-term births, 5 resulted in spontaneous abortion, 3 were electively terminated (none for medical reasons), and 13 were unknown or ongoing.³ Overall, the data on pregnancy exposure during clinical trials are insufficient to inform the risk associated with rimegepant.

In the proposed labeling, as of February 11, 2020 the Risk Summary in Section 8.1 states:

8.1 Pregnancy

¹ Dinatale M. Division of Pediatric and Maternal Health, FDA. The pregnancy and lactation labeling rule (PLLR). <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM520454.pdf> Accessed February 11, 2020

² Biohaven Pharmaceuticals, Inc. A Partially Double-blind, Randomized, Crossover Study to Assess the Effects of Rimegepant on QTc Interval Using a Therapeutic dose as well as a Supratherapeutic Dose Compared to Placebo and Moxifloxacin in Healthy Subjects: A Thorough QTc Study

³ Biohaven Pharmaceuticals, Inc. Rimegepant Appendix 8F Integrated Summary of Safety (ISS) Final version



Risk Summary

(b) (4)

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The estimated rate of major birth defects (2.2 to 2.9%) and miscarriage (17%) among deliveries to women with migraine are similar to rates reported in women without migraine.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data have suggested that women with migraine may be at increased risk of preeclampsia and gestational hypertension during pregnancy.

Data

Animal Data

(b) (4)

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)

Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

- Specific FDA-approved indication in pregnant women exists and exposure is expected
- No approved indication, but practitioners may use product off-label in pregnant women
- No approved indication, but there is the potential for inadvertent exposure before a pregnancy

is recognized

- No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

- Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
- Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †
- Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† *If checked, please complete [General ARIA Sufficiency Template](#).*

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

- Pregnancy registry with internal comparison group
- Pregnancy registry with external comparison group
- Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- Electronic database study with chart review
- Electronic database study without chart review
- Other, please specify: alternative study designs would be considered: e.g., retrospective cohort study using claims or electronic medical record data or a case control study

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

- Study Population
- Exposures
- Outcomes
- Covariates
- Analytical Tools

For any checked boxes above, please describe briefly:

Analytical Tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

Because broad-based signal detection is not currently available, other parameters were not assessed.

2.5. Please include the proposed PMR language in the approval letter.



The Division of Neurology 2 requests two PMRs related to pregnancy outcomes. As of February 11, 2020, the proposed PMR language for these are

PMR #1:

Conduct prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with migraine exposed to TRADENAME-ODT during pregnancy with two unexposed control populations: one consisting of women with migraine who have not been exposed to TRADENAME-ODT before or during pregnancy and the other consisting of women without migraine. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development will be assessed through at least the first year of life.

PMR #2:

Conduct a pregnancy outcomes study using a different study design than provided for in PMR XXXX-X (for example, a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to TRADENAME-ODT during pregnancy compared to an unexposed control population.

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/s/

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: February 19, 2020

To: Lana Chen
Regulatory Health Project Manager
Division of Neurology II (DN2)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Kelly Jackson, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Dhara Shah, PharmD, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): NURTEC-ODT (rimegepant sulfate)

Dosage Form and Route: orally disintegrating tablets, for sublingual use

Application Type/Number: NDA 212728

Applicant: Biohaven Pharmaceuticals, Inc.

1 INTRODUCTION

On June 27, 2019, Biohaven Pharmaceuticals, Inc. submitted for the Agency's review an Original New Drug Application (NDA) for rimegepant sulfate for the indication of the acute treatment of migraine in adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology II (DN2) on December 12, 2019 for DMPP and OPDP to review the Applicant's proposed, Patient Package Insert (PPI) for NURTEC-ODT (rimegepant sulfate) orally disintegrating tablets, for sublingual or oral use.

2 MATERIAL REVIEWED

- Draft NURTEC-ODT (rimegepant sulfate) PPI received on June 27, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 3, 2020.
- Draft NURTEC-ODT (rimegepant sulfate) Prescribing Information (PI) received on June 27, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 3, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: February 18, 2020

To: Heather Fitter, M.D.
Division of Neurology II (DN II)

Lana Chen, Regulatory Project Manager, DNP

Tracy Peters, Associate Director for Labeling, DNP

From: Dhara Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for rimegepant orally disintegrating tablets, for sublingual or oral use

NDA: 212728

In response to the DN II consult request dated December 12, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for rimegepant orally disintegrating tablets, for sublingual or oral use.

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DN II (Lana Chen) on February 3, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on February 7, 2020, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Dhara Shah at (240) 402-2859 or Dhara.Shah@fda.hhs.gov.

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/s/

DHARA SHAH
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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: February 15, 2020
Requesting Office or Division: Division of Neurology 2 (DN 2)
Application Type and Number: NDA (b) (4)
NDA 212728 (orally disintegrating tablet)
Product Name and Strength: rimegepant tablet, 75 mg
rimegepant orally disintegrating tablet, 75 mg
Applicant/Sponsor Name: Biohaven Pharmaceutical Holding Company Ltd
OSE RCM #: 2019-1380-2 and 2019-1377-2
DMEPA Team Leader: Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on February 7, 2020 for rimegepant tablet and rimegepant orally disintegrating tablet. The Division of Neurology 2 (DN 2) requested that we review the revised container labels and carton labeling (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review^a and a previous memorandum^b.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Karpow C. Label and Labeling Review for rimegepant and rimegepant orally disintegrating tablets (NDA (b) (4) and NDA 212728). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 OCT 29. RCM No.: 2019-1380 and 2019-1377.

^b Karpow C. Label and Labeling Review for rimegepant and rimegepant orally disintegrating tablets (NDA (b) (4) and NDA 212728). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 FEB 03. RCM No.: 2019-1380-1 and 2019-1377-1.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON FEBRUARY 7, 2020

(b) (4)



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BRIANA B RIDER
02/15/2020 08:33:02 AM

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research



Date: January 29, 2019

To: Billy Dunn, MD, Director
Divison of Neurology II

Through: Dominic Chiapperino, PhD, Director
Chad Reissig, PhD, Supervisory Pharmacologist
Controlled Substance Staff

From: Shalini Bansil, MD, Medical Officer
Edward Hawkins, PhD, Pharmacologist
Controlled Substance Staff

Subject: **Product name:** Rimegepant (BHV-3000, formerly BMS-927711)
Trade Name: (b) (4)
Dosages, routes: 75 mg orally, or sublingual, as needed, (b) (4)
NDA numbers: Rimegepant tablet NDA (b) (4) and Rimegepant Orally Disintegrating Tablets (ODT) NDA 212,728.
IND Number: 109,886
Indication: Acute treatment of migraine in adults.
Sponsor: Biohaven Pharmaceutical Holding Company, Ltd.
PDUFA Goal Date: February 27, 2020

Materials Reviewed:

- NDAs (b) (4) and 212,728 for Rimegepant

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I. SUMMARY

1. Background

This memorandum responds to a consult request by the Division of Neurology Products (DNP) (now renamed as Division of Neurology II, or DN2) dated August 2, 2019, to evaluate abuse-related preclinical and clinical data submitted by Biohaven Pharmaceutical Holding Company under NDAs (b) (4) and 212728, and IND109886 for rimegepant. Two rimegepant (BHV-3000) new drug applications (NDAs) are being evaluated concurrently for the acute treatment of migraine: rimegepant tablet, under NDA (b) (4) and rimegepant orally disintegrating tablet (ODT), under NDA 212728. Rimegepant is a new molecular entity, selective, high-affinity, orally-administered, small molecule calcitonin gene-related peptide (CGRP) receptor antagonist. The dose is 75 mg orally, as needed, (b) (4). The Sponsor proposes that rimegepant not be scheduled under the Controlled Substances Act (CSA). CSS concurs with the Sponsor that rimegepant should not be controlled under the CSA.

2. Conclusions

CSS has reviewed the nonclinical and clinical abuse-related data submitted in NDAs (b) (4) and 212728 for rimegepant and concludes that the drug does not have abuse potential and should not be

scheduled under the Controlled Substances Act (CSA). This conclusion is based on the data described below:

- Rimegepant is not similar in structure or mechanism of action to any substance controlled in the CSA.
- Rimegepant is a small molecule antagonist of the human calcitonin gene-related peptide (CGRP) receptor. It does not bind to ion channels, transporters, or receptors known to be associated with abuse potential.
- Rimegepant did not produce behaviors in animal toxicity or behavioral studies that are typically produced by known drugs of abuse.
- Rimegepant was not assessed in animal abuse potential studies, e.g., drug discrimination or self-administration studies. However, these studies are not necessary since rimegepant does not bind at receptors associated with abuse potential and did not produce behaviors associated with abuse potential in animals.
- Rimegepant was not assessed in animal tolerance and physical dependence studies.
- Abuse-related AEs were not observed in Phase 1-3 studies including at supratherapeutic doses.
- Rimegepant was not assessed for physical dependence or tolerance, given that the drug only required a limited abuse potential assessment from CSS perspective.

3. Recommendations

- Rimegepant does not require scheduling under the CSA at this time.
- Section 9, **Drug Abuse and Dependence**, is not required in the label.

II. DISCUSSION

1. Chemistry

1.1 Substance Information

Rimegepant hemisulfate sesquihydrate is the active pharmaceutical ingredient in (b) (4) tablets (75 mg). The tablets are designed for both oral administration and as sublingual dissolving tablets with a maximum dose of 75 mg. Rimegepant is also known by the developmental code BHV-3000 and the IPUAC name (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-piperidine-1-carboxylate hemisulfate sesquihydrate. Rimegepant hemisulfate sesquihydrate has a molecular weight of 610.63 g/mol, a chemical formula of $C_{28}H_{28}F_2N_6O_3 \cdot 0.5 H_2SO_4 \cdot 1.5 H_2O$, and a CAS # of 1374024-48-2. Rimegepant hemisulfate sesquihydrate is a white to off-white powder that is soluble in water (8.5 mg/mL at a pH of 1.4) and has a melting point rang of 163.3 to 206.8°C.

2. Nonclinical Pharmacology

2.1 Receptor Binding and Functional Assays

Rimegepant is a small molecule antagonist of the human calcitonin gene-related peptide (CGRP) receptor. Several binding and activity assays were conducted that determined that rimegepant has a $K_i = 32.9$ pM and an IC_{50} of 140.8 pM at the CGRP receptor. Study DT10062 determined that rimegepant does not bind with substantial activity at ion channels, transporters, or receptors known to be associated with abuse potential.

2.2 Safety Pharmacology/Metabolites

Rimegepant does not produce any major active circulating metabolites.

2.3 Findings from Safety Pharmacology and Toxicology Studies

The Sponsor conducted 3 studies to assess the cardiac, respiratory, and CNS safety pharmacology of rimegepant. There were no cardiac effects produced in monkeys after single or multiple doses of 50 mg/kg/day which produced exposures 17- and 24-fold greater than the therapeutic dose in humans. There were no respiratory effects at a dose of 100 mg/kg/day which produced exposures 115-fold higher than the human therapeutic exposure. In a 1-month oral toxicity study in rats, there were no CNS signs or effects at doses up to 100 mg/kg/day (AUC[0-24H] up to 431,000 ng•h/mL) which produced exposure levels 18- and a 115- times greater than exposures expected at the therapeutic dose in humans (75 mg).

2.4 Animal Behavioral Studies

No behavioral studies of abuse potential (e.g., drug discrimination or self-administration studies) were requested or conducted.

2.5 Tolerance and Physical Dependence Studies in Animals

No tolerance or physical dependence studies in animals were requested or conducted. See Section 4.5 for further details.

3. Clinical Pharmacology

3.1 Absorption, Distribution, Metabolism, Elimination (ADME)

The pharmacokinetics (PK) and ADME of rimegepant were assessed in rats, dogs, and monkeys. Since rimegepant did not produce signs of abuse potential in in vitro assays or in vivo behavioral assays, a discussion of the PK/ADME of the drug as it relates to abuse is not necessary. A complete discussion of the PK/ADME of the drug is assessed in the pharm/tox review.

Briefly, rimegepant dosed at 75 mg as ODT or as a tablet formulation produced bioequivalent exposures. The rate of absorption is faster with the ODT which produced a Tmax of 1.5 hours compared to the tablet which produced a Tmax of 1.9 hours. Both produced an absolute bioavailability of approximately 64%. The primary route of elimination is through the feces. Rimegepant is the primary circulating component in plasma with 88% to 92% unchanged parent present throughout the first 4 hours.

4. Clinical Studies

4.1 Human Abuse Potential Studies

The Sponsor did not conduct human abuse potential studies to assess the abuse potential of rimegepant.

4.2 Adverse Event Profile Through all Phases of Development

The Sponsor conducted 18 Phase 1 Studies and 5 Phase 2/3 studies during the clinical development program for rimegepant. All adverse events (AEs), including abuse-related AEs were coded to a Medical Dictionary for Regulatory Activities (MedDRA) and the MedDRA system organ class (SOC) and preferred term (PT). The following is a description and analysis of abuse-related AEs found during different phases of clinical development.

Phase 1 studies:

Single Dose studies

Table 1 displays the abuse-related AEs across the single dose, Phase 1 studies

Table 1: Abuse-related AEs Single dose Phase 1 Studies

Study Name/ Dose	Subjects (N)	Somnolence n (%)	Depressed mood n (%)
BHV-3000-102/75mg	Healthy (18)	2 (11)	2 (11)
BHV-3000-110/75 mg	Healthy (59)	2 (3.4)	0
BHV-3000-112/75mg	Healthy (32)	4 (12.5)	0
BHV-3000-113/75 mg	Healthy (52)	1 (1.9)	0
CN170006/300mg oral and IV	Healthy (8)	0	0
CN170004/300mg and 600 mg	Migraine patients (48)	0	0
BHV-3000-106/75 mg	Renally impaired subjects (36)	0	0
BHV-3000-107/75 mg	Hepatically impaired subjects (36)	0	0
BHV-3000-108/ 75 mg	Healthy (28)	1(3.6)	0
BHV-3000-109/75 mg and 300 mg	Healthy (38)	1 (2.6)	0

Drug-drug interaction studies (DDI): Abuse-related AEs in DDI studies with rimegepant are listed below:

BHV-3000-101: Depressed mood in one of 20 subjects (5%).

BHV-3000-103: Somnolence in one of 22 subjects (4.5%).

BHV-3000-104: Somnolence in one of 24 subjects (4.2%).

BHV-3000-105: Somnolence in one of 23 subjects (4.3%).

CN170002: No abuse-related AEs (N=18)

CN170007: No abuse-related AEs (N=14)

Multiple dose studies

CN170001: This was a Phase 1 single ascending dose (SAD) and multiple ascending dose (MAD) study in healthy subjects.

SAD: Subjects received single ascending doses of rimegepant from 25-1500 mg/day (N=42) or placebo (N=14). No abuse-related AEs were reported.

MAD: Subjects received doses of rimegepant from 75-600 mg/day (N=36) or placebo (N=12) for 14 days. No abuse-related AEs were reported.

BHV-3000-114: This was a Phase 1 study in healthy subjects (N=42) who received rimegepant 75 mg/day for 4 days. No abuse-related AEs were reported.

Conclusions for Phase 1 Studies: The only consistent abuse-related AE that was reported was somnolence (0-12.5%). Somnolence in isolation, without the occurrence of other abuse-related AEs, may not signal abuse potential. No abuse-related AEs were reported with IV administration of rimegepant. Doses as high as 1500 mg /day of rimegepant did not result in the occurrence of abuse-related AEs. Thus, the Phase 1 studies suggest that rimegepant does not have abuse potential.

Phase 2 and 3 studies:

Double-Blind, Randomized, Placebo-Controlled Dose-Ranging Trial of BMS-927711 for the Acute Treatment of Migraine Phase 2B. Study CN170003

The primary objective was to evaluate the efficacy of BMS-927711 compared with placebo in the acute treatment of migraine. This was a double-blind, randomized, multicenter, evaluation of the safety, efficacy, and dose-response of BMS-927711 compared to placebo, in the treatment of moderate to severe migraine headache. Subjects were randomized to receive placebo, sumatriptan 100 mg, or 1 of 6 doses of BMS-927711: 10 mg, 25 mg, 75 mg, 150 mg, 300 mg, or 600 mg. Eligible

subjects were dispensed one dose of randomized study medication and were sent home for 45 days to treat one migraine headache that met criteria for moderate to severe intensity (N = 811).

Table 2 displays the abuse-related AEs in study CN170003

Table 2: Abuse-related AEs Study CN170003

PT	BMS-927711 (N = 502)			Sumatriptan 100mg (N = 100)			Placebo (N = 209)		
	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)
Agitation	1	1	0.2	1	1	1	0	0	0
Depression	1	1	0.2	0	0	0	0	0	0
Disturbance in attention	0	0	0	0	0	0	1	1	0.48
Hyperhidrosis	0	0	0	1	1	1	0	0	0
Irritability	1	1	0.2	0	0	0	0	0	0
Somnolence	4	4	0.8	1	1	1	2	2	0.96

A Phase 3, Double-blind, Randomized, Placebo-controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) for the Acute Treatment of Migraine Study BHV 3000-301.

The primary objective was to evaluate the efficacy of rimegepant (75-mg tablet) compared to placebo in the acute treatment of migraine. BHV3000-301 was a Phase 3, double-blind, randomized, placebo-controlled, multicenter, outpatient evaluation of the efficacy and safety of a single dose of rimegepant compared to placebo in the treatment of moderate or severe migraine. Subjects were dispensed one dose of study medication consisting of a rimegepant 75-mg tablet or matching placebo and 1,095 subjects received treatment with rimegepant (546 subjects) or placebo (549 subjects).

Table 3 displays the abuse-related AEs in study BHV 3000-301

Table 3: Abuse-related AEs Study BHV3000-301

PT	Rimegepant, 75mg (N = 546)			Placebo (N = 549)		
	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)
Anxiety	0	0	0	2	2	0.36
Disorientation	0	0	0	1	1	0.18
Restlessness	1	1	0.18	0	0	0
Self-injurious ideation	1	1	0.18	0	0	0
Sensory disturbance	1	1	0.18	0	0	0
Somnolence	1	1	0.18	2	2	0.36

A Phase 3, Double-blind, Randomized, Placebo-controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) for the Acute Treatment of Migraine Study BHV3000-302.

The primary objective was to evaluate the efficacy of rimegepant (75-mg tablet) compared to placebo in the acute treatment of migraine. BHV3000-302 was a Phase 3, double-blind, randomized, placebo-controlled, multicenter, outpatient evaluation of the efficacy and safety of a single dose of rimegepant compared to placebo in the treatment of moderate or severe migraine. Subjects were dispensed one dose of study medication consisting of a rimegepant 75-mg tablet or matching placebo and 1,086 subjects received treatment with rimegepant (543 subjects) or placebo (543 subjects).

Table 4 displays the abuse-related AEs in study BHV3000-302

Table 4: Abuse-related AEs Study BHV3000-302

<i>PT</i>	<i>Rimegepant, 75mg (N = 543)</i>			<i>Placebo (N = 543)</i>		
	<i>Events</i>	<i>Number of subjects</i>	<i>Proportion (%)</i>	<i>Events</i>	<i>Number of subjects</i>	<i>Proportion (%)</i>
Depersonalisation/derealisation disorder	0	0	0	1	1	0.18
Disturbance in attention	1	1	0.18	0	0	0
Somnolence	5	4	0.74	2	2	0.37

A Phase 3, Double-blind, Randomized, Placebo-controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) Orally Disintegrating Tablet (ODT) for the Acute Treatment of Migraine Study BHV3000-303

The primary objective was to evaluate the efficacy of rimegepant (75 mg orally disintegrating tablet [ODT]) compared to placebo in the acute treatment of migraine. BHV3000-303 was a Phase 3, double-blind, randomized, placebo-controlled, multicenter, outpatient evaluation of the efficacy and safety of a single dose of rimegepant compared to placebo in the treatment of moderate or severe migraine. Subjects were dispensed 1 dose of study medication consisting of a rimegepant 75 mg ODT or matching placebo and 1,375 subjects received treatment with rimegepant (682 subjects) or placebo (693 subjects).

Table 5 displays the abuse-related AEs in study BHV3000-303

Table 5: Abuse-related AEs in BHV3000-303

<i>PT</i>	<i>Rimegepant, 75mg (N = 682)</i>			<i>Placebo (N = 693)</i>		
	<i>Events</i>	<i>Number of subjects</i>	<i>Proportion (%)</i>	<i>Events</i>	<i>Number of subjects</i>	<i>Proportion (%)</i>
Anxiety	2	2	0.29	0	0	0
Depressed mood	1	1	0.15	1	1	0.14
Depression	0	0	0	1	1	0.14
Feeling abnormal	1	1	0.15	0	0	0
Hyperhidrosis	1	1	0.15	0	0	0
Restlessness	1	1	0.15	0	0	0
Somnolence	2	2	0.29	1	1	0.14

A Multicenter, Open Label Long-Term Safety Study of BHV-3000 in the Acute Treatment of Migraine Phase 2/3 Study BHV3000-201

BHV3000-201 is an ongoing, multicenter, open-label, study in subjects with migraine. The objective is to assess the safety and tolerability of long-term use of rimegepant 75 mg, taken up to one tablet per calendar day. Subjects enrolled in the PRN (2-8) and PRN (9-14) groups were instructed that they could take a maximum of one rimegepant tablet per calendar day at the onset of a migraine of mild to severe intensity during the 52-week period. Subjects enrolled in the scheduled every other day (EOD) + PRN group were instructed to take one rimegepant tablet every other calendar day, regardless of whether or not they had a migraine on that day. If subjects in this group had a migraine on a non-dosing day, they could take a maximum of one rimegepant tablet per calendar day to treat a migraine. Therefore, subjects in this group could take a maximum of one rimegepant tablet per calendar day during the 12-week period. A total of 1,017 subjects, 481 subjects, and 286 subjects were enrolled and treated with rimegepant in the PRN (2-8), PRN (9-14), and scheduled EOD + PRN groups, respectively. Four subjects had an AE of accidental overdose related to a misunderstanding of the instructions regarding dosing. Additionally, the spouse of a study subject took an overdose of rimegepant in a suicide attempt. No adverse events were reported. The 90-day safety update of this study reported no additional AEs of concern.

Table 6 displays abuse-related AEs in study BHV3000-201

Table 6: Abuse-related AEs BHV3000-201.

<i>PT</i>	<i>Rimegepant, 75mg (N = 1784)</i>		
	<i>Events</i>	<i>Number of subjects</i>	<i>Proportion (%)</i>
Accidental overdose	4	4	0.22
Amnesia	4	4	0.22
Anxiety	21	21	1.18
Anxiety disorder	1	1	0.06
Cognitive disorder	4	3	0.17
Confusional state	3	3	0.17
Depressed mood	5	4	0.22
Depression	5	5	0.28
Disorientation	1	1	0.06
Disturbance in attention	1	1	0.06
Feeling abnormal	2	2	0.11
Hyperhidrosis	2	2	0.11
Irritability	1	1	0.06
Memory impairment	2	2	0.11
Mood swings	1	1	0.06
Sedation	1	1	0.06
Somnolence	24	23	1.29
Suicidal ideation	3	3	0.17

Conclusions for Phase 2/3 Studies: The Phase 2/3 studies showed low rates of abuse-related AEs in patients treated with rimegepant (less than 0.5%) and similar to the rates seen in placebo. There were no AEs related to euphoria. These findings further suggest that rimegepant does not have abuse potential.

4.3 Safety Profile

In the Phase 1 studies, the only consistent abuse-related AE that was reported was somnolence (0-12.5%). Somnolence in isolation, without the occurrence of other abuse-related AEs, may not signal abuse potential. No abuse-related AEs were reported with IV administration of rimegepant. Doses as high as 1500 mg /day of rimegepant did not result in the occurrence of abuse-related AEs. Thus, the Phase 1 studies suggest that rimegepant does not have abuse potential.

The Phase 2/3 studies showed low rates of abuse-related AEs in patients treated with rimegepant (less than 0.5%) and similar to the rates seen in placebo. There were no AEs related to euphoria. These findings suggest that rimegepant does not have abuse potential.

4.4 Evidence of Abuse, Misuse and Diversion in Clinical Trials

Investigators were required to monitor for possible cases of abuse of study medication and assess study medication accountability discrepancies. In all Phase 2/3 studies except BHV3000-201 subjects were dispensed only one tablet of study medication. In BHV3000-201 subjects were dispensed a 30-tablet bottle of rimegepant and instructed that they could self-administer rimegepant as needed up to once per calendar day to treat migraine of any severity. The Sponsor reports that in this setting of subject access to 30 tablets of rimegepant per month for up to 52 weeks, there was little evidence to suggest misuse, overuse, or abuse of rimegepant based on careful review of AEs, dosing frequencies, and drug accountability.

4.5 Tolerance and Physical Dependence Studies in Humans

The Sponsor did not conduct studies on physical dependence. Rimegepant is to be administered as a single dose on an as needed basis and not as a daily dose for long-term use. Additionally, assessment of abuse-related AEs during the clinical development program revealed the absence of such AEs. Therefore, assessment of physical dependence is not essential to evaluate the abuse potential of rimegepant. The Sponsor's lack of evaluation of physical dependence in humans is acceptable from CSS perspective.

5. Regulatory Issues and Assessment

Based on the lack of signals of abuse potential from in vitro binding and animal data and the lack of abuse-related AEs in Phase 1-3 studies during clinical development, we agree with the Sponsor that rimegepant should not be controlled under the CSA. Section 9, **Drug Abuse and Dependence**, is not required in the label.

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/s/

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: February 3, 2020
Requesting Office or Division: Division of Neurology 2 (DN 2)
Application Type and Number: NDA (b) (4)
NDA 212728 (orally disintegrating tablet)
Product Name and Strength: rimegepant tablet, 75 mg
rimegepant orally disintegrating tablet, 75 mg
Applicant/Sponsor Name: Biohaven Pharmaceutical Holding Company Ltd
OSE RCM #: 2019-1380-1 and 2019-1377-1
DMEPA Safety Evaluator: Celeste Karpow, PharmD, MPH
DMEPA Team Leader: Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on December 30, 2019 for rimegepant tablet and rimegepant orally disintegrating tablet. The Division of Neurology 2 (DN 2) requested that we review the revised container labels and carton labeling (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective. We identified the following areas of necessary improvement that may contribute to medication errors:

^a Karpow C. Label and Labeling Review for rimegepant and rimegepant orally disintegrating tablets (NDA (b) (4) and NDA 212728). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 OCT 29. RCM No.: 2019-1380 and 2019-1377.

Container label for the (b) (4) Blister Carton labeling for 8-count ODT, and Professional Sample Blister Carton labeling 2-count ODT

- It is not indicated if the month (MM) of the expiration date will be denoted using numerical characters (e.g., 06), or alphabetical characters (e.g., JU) which might lead to misinterpretation or deteriorated drug medication errors.
- The dosage form lacks prominence.

Blister Carton labeling for 8-count ODT and Professional Sample Blister Carton labeling 2-count ODT

- The principal display panel (PDP) does not describe the milligram amount of drug per single unit (75 mg); therefore, there might be confusion as to how much product is contained in a single unit compared to the total contents of the entire blister card and might lead to wrong dose errors.

Blister Carton labeling for 8-count ODT

- The placeholder for the product identifier (serial number, expiration date, lot number) has been removed from the blister carton labeling for the 8-count ODT.



3 RECOMMENDATIONS FOR BIOHAVEN PHARMACEUTICAL HOLDING COMPANY LTD

We recommend the following be implemented prior to approval of NDA (b) (4) and NDA 212728:

- A. Container label for the (b) (4) Blister Carton labeling for 8-count ODT, and Professional Sample Blister Carton labeling 2-count ODT
1. You request to keep the human-readable expiration date format as “YYYY-MM”. However, you have not indicated whether you intend to denote the month (MM) using numerical characters (e.g., 06) or alphabetical characters (e.g., JU). Therefore, we are unable to assess the acceptability of the proposed expiration date format from a medication safety perspective. Please clarify whether you

^b Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

intend to use numerical or alphabetical characters to denote the month in your proposed expiration date format.

2. The dosage form lacks prominence. Per our Draft Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, the established name for drug products should include the finished dosage form^c. Per 21 CFR 201.10(g)(2), the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name. Ensure the established name (active ingredient and finished dosage form) appears in accordance with 21 CFR 201.10(g)(2), taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
- B. Blister Carton labeling for 8-count ODT [REDACTED] (b) (4) Blister Carton labeling for 2-count ODT
1. The strength has been revised on the side panels to read: "75 mg per orally disintegrating tablet". We are concerned this statement may be overlooked on the side panel. Per our Draft Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*^c, the product strength on the principal display panel (PDP) and other panels of the blister carton labeling should describe the milligram amount of drug per single unit so that there is no confusion as to how much product is contained in a single unit compared to the total contents of the entire blister card. Based on our postmarketing experience, we are concerned that the entire contents of the blister pack (i.e., [REDACTED] (b) (4) 8 orally disintegrating tablets) may be mistaken for a 75 mg dose. Revise the strength statement [REDACTED] (b) (4) to state "75 mg per orally disintegrating tablet" to make it clear that the designated strength is per one unit. Consider increasing the prominence of this statement "75 mg per orally disintegrating tablet" on the PDP [REDACTED] (b) (4) or address this concern by other means.
- C. Blister Carton labeling for 8-count ODT
1. The placeholder for the product identifier (serial number, expiration date, lot number) has been removed from the blister carton labeling for the 8-count ODT. Therefore, we are unable to assess the product identifier from a medication safety perspective. If you determine that the product identifier requirements^d apply to your product's labeling, we recommend you add the placeholder for the product identifier to the carton labeling. Additionally, the lot number and expiration date are required per 21 CFR 201.10(i)(1) and 21 CFR 211.137,

^c Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

^d The draft guidance is available from: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>

respectively. Ensure that the lot number and expiration date are present. Lastly, ensure the lot number is clearly differentiated from the expiration date.

(b) (4)

(b) (4)

13 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS)
immediately following this page

^e Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

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/s/

CELESTE A KARPOW
02/03/2020 12:33:39 PM

BRIANA B RIDER
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Clinical Inspection Summary

Date	10 January 2020
From	Cheryl Grandinetti, PharmD, Clinical Pharmacologist Phillip Kronstein, MD, Acting Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Lana Chen, RPM Laura Jawidzik, MD, Clinical Reviewer Heather Fitter, MD, Clinical Team Leader Billy Dunn, MD, Division Director, Division of Neurology Products
NDA #	(b) (4) and 212728
Applicant	Biohaven Pharmaceuticals, Inc
Drug	Rimegepant
NME	Yes
Proposed Indication	For the acute treatment of migraines in adult patients
Consultation Request Date	28 August 2019
Summary Goal Date	17 January 2020
Action Goal Date	27 February 2020
PDUFA Date	27 February 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Halverson, Harper, Kroll, Patel, Rosenberg, Brandes, and Shoemaker, and the study sponsor, Biohaven Pharmaceuticals, Inc. were inspected in support of these two NDAs (b) (4) and 212728).

The inspection of Dr. Brandes' site (Site 002) for Protocol BHV3000-303 found significant data integrity issues and concerns related to good clinical practice (GCP) noncompliance, including but not limited to a lack of source documents necessary to verify the study data collected at the site. Of note, in a letter dated 9 November 2018, Biohaven Pharmaceuticals, Inc. informed FDA of GCP noncompliance at Dr. Brandes' site. In an email dated 13 November 2018, the Division of Neurology Products recommended that the sponsor conduct a sensitivity analysis on the primary and key secondary endpoints with regard to the data from this site. Biohaven conducted the sensitivity analysis, and included the results in the Clinical Study Report for Protocol BHV3000-303, dated 16 April 2019, submitted to FDA.

The inspection of the sponsor identified issues with the electronic patient-reported outcome (ePRO) devices used during the trial, including (1) design and validation issues, including inadequate user acceptance testing (UAT) of the ePRO devices, and (2) insufficient training and retraining of all subjects and study personnel on the use of the ePRO devices. These issues contributed to a number of missing post-migraine assessments but were limited in scope due to Biohaven's centralized monitoring efforts that facilitated quick identification and resolution of the ePRO device software deficiencies.

Notwithstanding these observations, the studies appear to have been conducted adequately. The study data, including the primary efficacy endpoint data for the three protocols (BHV3000-301, BHV3000-302, and BHV3000-303), otherwise appear acceptable in support of the respective indication.

II. BACKGROUND

This application was submitted in support of the use of rimegepant for the acute treatment of migraines in adult patients. The key studies supporting the two applications were the following:

- BHV3000-301: A Phase 3, double-blind, randomized, placebo-controlled, safety and efficacy trial of BHV-3000 (rimegepant) for the acute treatment of migraine
- BHV3000-302: A Phase 3, Double-blind, Randomized, Placebo-controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) for the Acute Treatment of Migraine
- BHV3000-303: A Phase 3, Double-blind, Randomized, Placebo-controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) Orally Disintegrating Tablet (ODT) for the Acute Treatment of Migraine

Protocol BHV3000-301

- *Subjects:* 1,485 subjects were enrolled in this study. A total of 1,162 subjects were randomized to the rimegepant (582 subjects) or placebo (580 subjects) groups, of whom 1,095 subjects received treatment with rimegepant (546 subjects) or placebo (549 subjects)
- *Sites:* 50 sites in the United States
- *Study Initiation and Completion Dates:* The first subject was enrolled on 18 Jul 2017 and the last subject completed 26 Jan 2018
- *Database lock* occurred on 01 Mar 2018

Protocol BHV3000-302

- *Subjects:* 1,499 subjects were enrolled in this study. A total of 1,186 subjects were randomized to the rimegepant (594 subjects) or placebo (592 subjects) groups, of whom 1,086 subjects received treatment with rimegepant (543 subjects) or placebo (543 subjects)
- *Sites:* 50 sites in the United States
- *Study Initiation and Completion Dates:* The first subject was enrolled on 27 Jul 2017 and the last subject completed 31 Jan 2018
- *Database lock* occurred on 06 Mar 2018

Protocol BHV3000-303

- *Subjects:* 1,811 subjects were enrolled in this study. A total of 1,466 subjects were randomized to the rimegepant (732 subjects) or placebo (734 subjects) groups, of whom 1375 subjects received treatment with rimegepant (682 subjects) or placebo (693 subjects)
- *Sites:* 69 sites in the United States and 67 sites enrolled at least 1 subject
- *Study Initiation and Completion Dates:* The first subject was enrolled on 27 Feb 2018 and the last subject completed 15 Oct 2018
- *Database lock* occurred on 21 Nov 2018

All three protocols were identical in study design; however, Protocol BHV3000-303 used a an orally disintegrating tablet (ODT) formulation of rimegepant and placebo. They were phase 3, double-blind, randomized, placebo-controlled, safety and efficacy trials of rimegepant for the acute treatment of migraine. The primary objective was to evaluate the efficacy of rimegepant 75 mg tablet (or 75 mg ODT for protocol BHV3000-303) compared with matching placebo in the acute treatment of migraine as measured by pain freedom and by freedom from the most bothersome symptom (MBS)

associated with migraine at two hours post dose.

Subjects received 1 dose to treat 1 migraine headache of moderate or severe intensity within 45 days after randomization (baseline visit). Subjects were provided the study medication at randomization (baseline visit) and took the study drug at the time of the moderate or severe migraine onset after answering questions regarding their migraine symptoms on an electronic diary (eDiary).

The co-primary efficacy endpoint was

- Pain freedom at 2 hours post dose— to assess pain freedom, subjects were given an eDiary to record their migraine pain score using a 4-point numeric rating scale (no pain, mild pain, moderate pain, severe pain).
- Freedom from the most bothersome symptom (MBS) 2 hours post-dose—to assess freedom from the MBS, subjects were asked to identify their most bothersome symptom (nausea, phonophobia or photophobia) on the eDiary at the onset of the migraine to be treated. The MBS must have been identified before the subject took study medication. The migraine associated symptom of photophobia, phonophobia, or nausea was then assessed on a 2-point scale (present or absent) using the eDiary. If a subject reported the presence of a symptom, the subject was then asked to rate the severity of the symptom on a 4-point scale (none, mild, moderate or severe).

Efficacy assessments of pain and MBS were assessed at the onset of moderate or severe migraines and at 15, 30, 45, 60, and 90 minutes, and 2, 3, 4, 6, 8, 24 and 48 hours post dose.

A *secondary efficacy endpoint* of interest to the Division of Neurology Products is the probability of the subject requiring rescue medication within 24 hours after administration of the study drug. The subject's use of rescue medication was recorded by the subject in a paper diary. Patients were to keep track of their concomitant medications throughout the study and report them to the study personnel at the End of Treatment Visit. Any medication taken for recurrent headache should have been documented.

Rationale for Site Selection

The clinical sites were chosen primarily based on numbers of enrolled subjects, site efficacy, low reporting of adverse events, high incidence of protocol violations, and prior inspectional history.

III. RESULTS (by site):

1. Philip Halverson, MD
BHV3000-301 (NDA (b) (4) Site #012
BHV3000-303 (NDA 212728); Site #042
2085 Campus Drive Suite 435
Clinical Research Institute, Inc.
Plymouth, MN 55441

At this site for Protocol BHV3000-301, 12 subjects were screened and enrolled, and 11 were randomized, all of whom completed the study. For Protocol BHV3000-303, 5 subjects were screened and enrolled, all of whom were randomized and completed the study. Records reviewed included, but were not limited to, the study protocol and amendments, IRB submissions and approvals, subject eligibility criteria, informed consent, randomization procedures, source data and records, electronic case report forms, electronic diary data and paper rescue medication diaries, drug accountability, adverse event reporting, protocol deviations, and monitor logs and follow-up letters. An audit of the study records for the 11 subjects randomized in Protocol BHV3000-301 was conducted. In addition, a limited review of eDiary study records for all 5 subjects randomized in Protocol BHV3000-303 was conducted.

There was no evidence of under-reporting of adverse events. The electronic diary source data for the primary efficacy

endpoint and the subject paper diaries for tracking the use of concomitant rescue medications were reviewed and verified against the data listings provided by the sponsor for all randomized subjects in the two trials. No discrepancies were noted.

2. Charles Harper, MD
BHV3000-301 (NDA (b) (4) Site #013
1410 N 13th Street Suite 5
Meridian Clinical Research -Norfolk
Norfolk, NE 68701

At this site for Protocol BHV3000-301 , 32 subjects were screened and enrolled, 25 were randomized, and 24 subjects completed the study. One subject withdrew consent. Records reviewed included, but were not limited to, the study protocol and amendments, IRB submissions and approvals, subject eligibility criteria, informed consent, randomization procedures, source data and records, electronic case report forms, electronic diary data and paper rescue medication diaries, drug accountability, adverse event reporting, protocol deviations, and monitor logs and follow-up letters. An audit of the study records for all 25 subjects who were randomized was conducted.

The electronic diary source data for the primary efficacy endpoint and the subject paper diaries for tracking the use of concomitant rescue medications were reviewed and verified against the data listings provided by the sponsor for all 25 subjects randomized. No discrepancies were noted.

3. Robin Kroll, MD
BHV3000-301 (NDA (b) (4) Site #017
3216 NE 45th Place Suite 100
Seattle Women's Health, Research & Gynecology
Seattle, WA 98105

At this site for Protocol BHV3000-301, 28 subjects were screened and enrolled, 20 were randomized, and 18 subjects completed the study. One subject was randomized but was lost to follow-up, and another was randomized but did not have a qualifying migraine within 45 days after randomization. Records reviewed included, but were not limited to, the study protocol and amendments, IRB submissions and approvals, subject eligibility criteria, informed consent, randomization procedures, source data and records, electronic case report forms, electronic diary data and paper rescue medication diaries, drug accountability, adverse event reporting, protocol deviations, and monitor logs and follow-up letters. An audit of the study records for 20 subjects who were randomized was conducted.

There was no evidence of under-reporting of adverse events. The electronic diary source data for the primary efficacy endpoint and the subject paper diaries for tracking the use of concomitant rescue medications were reviewed and verified against the data listings provided by the sponsor for all 20 subjects randomized. No discrepancies were noted.

4. Nirav Patel, MD
BHV3000-302 (NDA (b) (4) Site #035
2600 Redondo Ave. Suite 500
Collaborative Neuroscience Network, LLC
Long Beach, CA 90806

At this site for Protocol BHV3000-302, 39 subjects were screened, 27 were randomized, and 25 subjects completed the study. One subject was lost to follow-up, and one subject withdrew early due to a family death. Records reviewed included, but were not limited to, the study protocol and amendments, IRB submissions and approvals, subject eligibility criteria, informed consent, randomization procedures, source data and records, electronic case report forms, electronic diary data and paper rescue medication diaries, drug accountability, adverse event reporting, protocol deviations, and monitor logs and follow-up letters. A complete audit of the study records for 25% of subjects who were randomized was conducted.

There was no evidence of under-reporting of adverse events. The electronic diary source data for the primary efficacy endpoint and the subject paper diaries for tracking the use of concomitant rescue medications were reviewed and verified against the data listings provided by the sponsor for all 27 subjects randomized. No discrepancies were noted.

5. David Rosenberg, MD
BH3000-302 (NDA (b) (4) Site #017
4281 Katella Avenue Suite 115
Pharmacology Research Institute
Los Alamitos, CA 90720

At this site for Protocol BH3000-302, 20 subjects were screened and enrolled and 19 were randomized, all of whom completed the study. Records reviewed included, but were not limited to, the study protocol and amendments, IRB submissions and approvals, subject eligibility criteria, informed consent, randomization procedures, source data and records, electronic case report forms, electronic diary data and paper rescue medication diaries, drug accountability, adverse event reporting, protocol deviations, and monitor logs and follow-up letters. An audit of the study records for the 19 subjects randomized by this site was conducted.

There was no evidence of under-reporting of adverse events. The electronic diary source data for the primary efficacy endpoint and the subject paper diaries for tracking the use of concomitant rescue medications were reviewed and verified against the data listings provided by the sponsor for all 19 subjects randomized. No discrepancies were noted.

6. Jan Brandes, MD
BH3000-303 (NDA 212728); Site #002
300 20th Avenue North Suite 106
Nashville Neuroscience Group
Nashville, TN 37203

At this site for Protocol BH3000-303, 24 subjects were screened and enrolled, and 22 were randomized, all of whom completed the study. Records reviewed included, but were not limited to, the study protocol and amendments, IRB submissions and approvals, subject eligibility criteria, informed consent, randomization procedures, source data and records, electronic case report forms, electronic diary data, drug accountability, adverse event reporting, protocol deviations, and monitor logs and follow-up letters. A complete audit of the study records for all subjects randomized was conducted.

Several significant deficiencies were noted, and a Form FDA-483 was issued to Dr. Brandes at the conclusion of the inspection. These deficiencies included (but were not limited to) failure to maintain adequate case histories with respect to observations and data pertinent to the investigation and to adequately supervise employees who performed study-related tasks. Specifically, Dr. Brandes and her delegated study staff did not maintain adequate source documents, such as physician progress notes, nurses' notes, and other medical records that were necessary to verify the study data recorded in the EDC system and on the study paper worksheets. In addition, for all 22 subjects randomized, site personnel did not enter or record study data in the EDC system or the paper study worksheets in a contemporaneous manner for the screening, baseline and/or end-of treatment visits. In many cases, the data were entered in the EDC system and recorded on paper study worksheets approximately 2 months after the subjects' screening, baseline and end-of-treatment visits.

In addition, Dr. Brandes delegated the study task of confirming eligibility to study coordinators that had no medical training or experience, without a qualified second person reviewing and signing the documents. A number of protocol violations were also noted.

Reviewer's comments: On 11 July 2018, the sponsor put this site on enrollment hold after the site's main study coordinator abruptly resigned. Biohaven Pharmaceuticals, Inc. informed FDA of significant GCP noncompliance at Dr.

Brandes' site in a letter dated 9 November 2018. In an email dated 13 November 2018, the Division of Neurology Products recommended that Biohaven conduct a sensitivity analysis on the primary and key secondary endpoints with regard to the data from this site. Biohaven conducted the sensitivity analysis, and included the results in the Clinical Study Report for Protocol BHV3000-303, dated 16 April 2019, submitted to FDA. Significant GCP noncompliance issues were also observed during the inspection of this site, including the lack of source documents necessary to verify the study data.

7. James Shoemaker, MD
BHV3000-303 (NDA 212728); Site #036
77 W. Granada Blvd.
Ormond Medical Arts Pharmaceutical Research
Ormond Beach, FL 32174

At this site, 44 subjects were screened and enrolled, 42 were randomized, and 39 subjects completed the study. Three subjects were discontinued from the study. Records reviewed included, but were not limited to, the study protocol and amendments, IRB submissions and approvals, subject eligibility criteria, informed consent, randomization procedures, source data and records, electronic case report forms, electronic diary data and paper rescue medication diaries, drug accountability, adverse event reporting, protocol deviations, and monitor logs and follow-up letters. An audit of the study records for the 42 subjects who were randomized was conducted.

There was no evidence of under-reporting of adverse events. The electronic diary source data for the primary efficacy endpoint and the subject paper diaries for tracking the use of concomitant rescue medications were reviewed and verified against the data listings provided by the sponsor for the 42 subjects randomized. No discrepancies were noted.

8. Biohaven Pharmaceuticals, Inc.
215 Church Street
New Haven, CT 06510

The inspection of the sponsor, Biohaven Pharmaceuticals, Inc focused on the control, oversight, and management of Protocols BHV3000-301, BHV3000-302, and BHV3000-303. The inspection covered roles and responsibilities, organization and its personnel, registration of studies on clinicaltrials.gov, selection and monitoring of clinical investigators, selection of monitors, monitoring procedures and activities, quality management, adverse event reporting, process for managing protocol deviations, data collection, handling, and management, record retention, financial disclosure, and test article accountability. Records reviewed during the inspection included investigator agreements, vendor agreements, and contracts, written standard operating procedures, documentation of protocol deviations, validation and other documentation related to the operational use of the electronic data capture (EDC) systems (i.e., rEDCap system, Medidata Rave, IWRS/IXRS, and StudyWorks and ePRO devices), adverse event reporting, drug accountability, relevant communication and correspondence, and monitoring activities.

For the 3 protocols, Biohaven Pharmaceuticals, Inc was responsible for site selection, regulatory documentation collection, study oversight, writing of the protocol, statistics, medical writing, and maintenance and retention of study related documents in their electronic Trial Master File. Biohaven contracted with (b) (4) for Protocols BHV3000-301 and BHV3000-302 and (b) (4) for Protocols BHV3000-303. Among other responsibilities, these contract research organizations were responsible for site monitoring and data management (e.g., EDC systems, validation, CRF creation, generation of listings for data review, coding of data, review of data, query generation and resolution, audit of database).

The sponsor also contracted with (b) (4) to supply the ePRO devices and to manage the ePRO data in (b) (4) online portal (b) (4). The sponsor reported to FDA in the Clinical Study Report issues related to the use of the ePRO devices that contributed to a number of the missing post-migraine assessment data for the three protocols as noted below in Table 1.

Table 1: Missing post migraine assessment data

Study	Percentage of subjects with missing eDiary pain data at 2 hours post-dose	Percentage of subjects with Missing eDiary MBS data at 2 hours post-dose
BHV3000-301	4.5%	6.5%
BHV3000-302	4.3%	6.7%
BHV3000-303	3.6%	5.2%

OSI further investigated the device issues and root cause(s) for the missing data during the sponsor inspection. In summary, most of the missing assessments resulted from (1) device design and validation issues, including inadequate UAT of the ePRO devices, and (2) insufficient training and retraining of all subjects and study personnel on the use of the ePRO devices.

Reviewer's comment: There were ePRO device design and validation issues as well as insufficient training and retraining of study subjects and study personnel on the use of ePRO devices. Biohaven acknowledged the training and retraining issues and promised to make improvements in future trials. These issues contributed to a number of missing post-migraine assessments but were limited in scope due to Biohaven's centralized monitoring efforts that facilitated quick identification and resolution of the ePRO device software deficiencies.

{See appended electronic signature page}

Cheryl Grandinetti, Pharm.D.
Clinical Pharmacologist
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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CONCURRENCE:

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Interdisciplinary Review Team for Cardiac Safety Studies

QT Consultation Review

Submission	NDA (b) (4) / 212728
Submission Number	SN0001 SDN001 / SN0003 SDN004
Submission Date	6/27/2019
Date Consult Received	7/15/2019
Clinical Division	DNP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult regarding the sponsor's QT evaluation. The IRT reviewed the following materials:

- Previous QT-IRT review dated 2/17/2017 ([link](#)) and 6/18/2018 ([link](#)) under IND 109886 in DARRTS;
- Highlights of clinical pharmacology and cardiac safety under NDA (b) (4) (SN0003 / SDN004; [link](#));
- Summary of Clinical Pharmacology Studies under NDA (b) (4) (SN0001 / SDN002; [link](#));
- Sponsor's proposed product label (SN0001 / SDN002; [link](#)); and
- TQT study report BHV3000-109 under NDA (b) (4) (SN0001 / SDN002; [link](#)).

1 SUMMARY

No significant QTc prolongation effect was detected in this QT assessment of rimegepant.

The effect of rimegepant was evaluated in the TQT study BHV3000-109. The highest dose that was evaluated was a single dose of 300 mg, which covers the worst case exposure scenario (i.e., severe hepatic impairment, Section 3.1). The data were analyzed using concentration-QTc as the primary analysis, which did not suggest that rimegepant is associated with significant QTc prolonging effect - see Table 1 for overall results. The findings of this analysis are further supported by the available nonclinical data (Section 3.1), by-time analysis (Section 4.3), and categorical outlier analysis (Section 4.4).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG parameter	Treatment	Concentration	$\Delta\Delta$ (ms)	90% CI (ms)
QTc	Rimegepant 75 mg	874.4 ng/mL	0.6	(0.1 to 1.2)
QTc	Rimegepant 300 mg	4895.2 ng/mL	0.8	(-0.6 to 2.2)

Rimegepant tablet and orally disintegrating tablets are being developed for the acute treatment of migraine in adults. The recommended dose is 75 mg as needed, with or without food, (b) (4). High-fat meal decreases C_{max} by 33-41%. Accumulation at the maximum recommended dose level (i.e. 75 mg QD) is not expected to be significant given the short half-life (i.e. approximately 8 hours, Tables 23 and 24 in

the Summary of Clinical Pharmacology Studies; 11 hours based on population PK analysis). The highest exposure scenario is that in subjects with severe hepatic impairment (i.e. 90% increase in C_{max}). Based on the population PK analysis, the predicted steady state C_{max} in a typical subject taking 75 mg rimegepant tablet is 681 ng/mL or 714 ng/mL for the table and the oral disintegrating tablet, respectively. This TQT study covers the worse-case exposure scenario for rimegepant tablets.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 PROPOSED LABEL

Below are proposed edits from the IRT to the label submitted to SN0001 ([link](#)). Our changes are highlighted ([addition](#), ~~deletion~~). We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

 (b) (4)
At a single dose 4 times the recommended dose (75 mg), rimegepant does not prolong the QT interval to any clinically relevant extent. (b) (4)


Reviewer's comments: We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

The IRT reviewed the QT assessment proposal previously (under IND 109886, dated 06/18/2018 in DARRTS). The study protocol and QT assessment plan was deemed acceptable.

- The primary endpoint was to evaluate the effect of rimegepant concentrations vs. QTcF interval.
- The secondary endpoints were other electrocardiogram (ECG) parameters (heart rate, PR interval, QRS interval, and T and U wave morphology).

- The primary analysis was concentration-QTc analysis.
- There was no change in therapeutic (75 mg) or suprathreshold (300 mg) dose, in the fasted state, as previously proposed. The suprathreshold dose covered the worst-case exposure scenario, i.e., severe hepatic impairment (i.e. 90% increase in C_{max}). The sponsor also reported that the rimegepant exposure was generally higher (25%-67% increase) during the migraine period than the non-migraine period.

3.1.2 Nonclinical

In in vitro cardiovascular safety assessments, rimegepant was a weak blocker of the human ether-a-go-go related gene (hERG)/IKr (potassium) channel (flux assay IC₅₀ = 32 ± 9.4 μM), had only weak activity in the patch clamp assay (14 and 27% inhibition at 10 and 30 μM, respectively), and had no effects on the action potentials of rabbit Purkinje fibers at concentrations up to 30 μM (highest concentration tested). Accounting for human protein binding (96% bound), based on C_{max} from PPK of 1.20 μM at the 75 mg dose, the ratio between hERG IC₅₀ and free C_{max} is >667-fold.

3.2 SPONSOR'S RESULTS

3.2.1 By-time Analysis

Rimegepant excluded the 10 ms threshold at the therapeutic (75 mg) and suprathreshold (300 mg) dose levels for ΔΔQTcF. Sponsor's analysis used a linear mixed-effects model with change from baseline QTcF (ΔQTcF) as the dependent variable, period, sequence, time, treatment (rimegepant, moxifloxacin and placebo), and time-by-treatment interaction as fixed effects, and baseline QTcF as a covariate. The results of the reviewer's analysis are similar to the sponsor's results. Please see Section 4.3 for additional details.

3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin in by-time analysis. The results of the reviewer's analysis are similar to the sponsor's results. Please see Section 4.3 for additional details.

3.2.1.1.1 QT bias assessment

Not applicable.

3.2.2 Categorical Analysis

No subject had QTcF >480 ms. No subject had ΔQTcF >60 ms. The results of the reviewer's analysis are similar to the sponsor's results. Please see Section 4.4 for additional details.

3.2.3 Safety Analysis

There were no deaths, SAEs or AEs leading to discontinuation reported in this study.

There were no cardiac-related AEs or AEs related to QTc prolongation.

3.2.4 Exposure-Response Analysis

The sponsor applied linear mixed effect modeling using $\Delta\Delta\text{QTcF}$ as the dependent variable, rimegepant concentration and centered baseline as the fixed effect covariate and included subjects as a random effect for both intercept and slope. A linear model with an intercept was selected as the final model. Both the slope and the intercept of the concentration- QTc relationship was not statistically significant. The predicted $\Delta\Delta\text{QTcF}$ effect using the sponsor's model was 0.45 msec (90% CI: -1.11, 2.01) and 0.54 msec (90% CI: -0.96, 2.05) at the observed geometric mean peak plasma level after dosing with rimegepant 75 mg (885 ng/mL) and 300 mg (4963 ng/mL), respectively.

The results of the reviewer's analysis are similar to the sponsor's results. Please see Section 4.5 for additional details.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no significant increases or decreases in heart rate (i.e. absolute mean change in HR <10 bpm) were observed (see Sections 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Waveforms from the ECG warehouse were reviewed. Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT bias assessment

Not applicable.

4.3 CENTRAL TENDENCY ANALYSIS

4.3.1 QTc

The primary analysis used Mixed Effect Model Repeat Measurement (MMRM) to analyze the $\Delta\Delta\text{QTcF}$. Figure 1 displays the time profile of $\Delta\Delta\text{QTcF}$ for different treatment groups. The $\Delta\Delta\text{QTcF}$ values with the largest upper bounds by treatment are shown in

Table 2.

Figure 1: Mean and 90% CI of $\Delta\Delta\text{QTcF}$ Timecourse (unadjusted CIs)

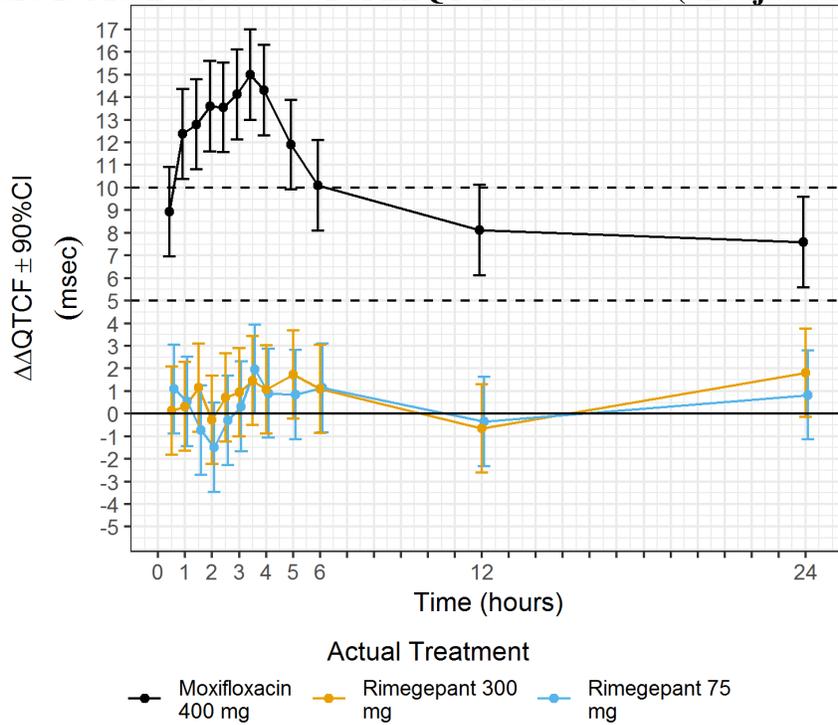


Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for $\Delta\Delta\text{QTcF}$

Treatment	Time (h)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
Rimegepant 75 mg	3.5	2.0	(0.0 to 3.9)
Rimegepant 300 mg	24	1.8	(-0.1 to 3.8)

4.3.1.1 Assay sensitivity

The same statistical model was used to analyze moxifloxacin on the $\Delta\Delta\text{QTcF}$ effects. The time-course of changes in $\Delta\Delta\text{QTcF}$ is shown in Figure 1. The largest lower confidence interval was 12.3 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study (Table 3).

Table 3: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bound for Moxifloxacin 400 mg

Treatment	Time (h)	$\Delta\Delta\text{QTcF}$ (ms)	97.5% CI (ms)
Moxifloxacin 400 mg	3.5	15.0	(12.3 to 17.7)

4.3.2 HR

Figure 2 displays the time profile of $\Delta\Delta\text{HR}$ based on MMRM analysis. The $\Delta\Delta\text{HR}$ values with the largest upper bounds by treatment are shown in Table 4.

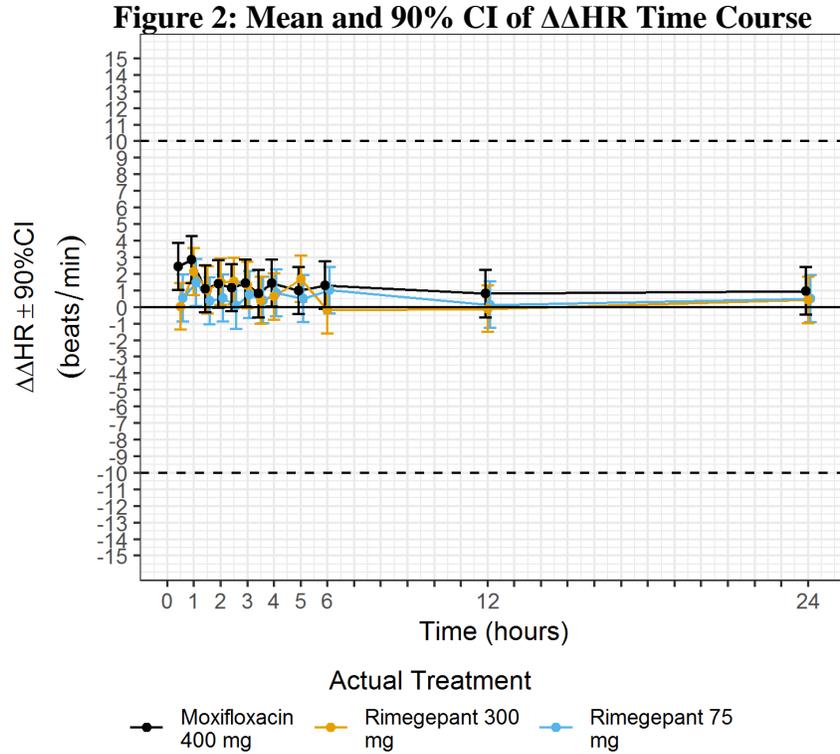


Table 4: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for $\Delta\Delta\text{HR}$

Treatment	Time (h)	$\Delta\Delta\text{HR}$ (bpm)	90% CI (ms)
Rimegepant 75 mg	1	1.5	(0.1 to 2.9)
Rimegepant 300 mg	1	2.1	(0.7 to 3.5)

4.3.3 PR

Figure 3 displays the time profile of $\Delta\Delta\text{PR}$ based on MMRM analysis. The $\Delta\Delta\text{PR}$ values with the largest upper bounds by treatment are shown in Table 5.

Figure 3: Mean and 90% CI of $\Delta\Delta PR$ Time Course

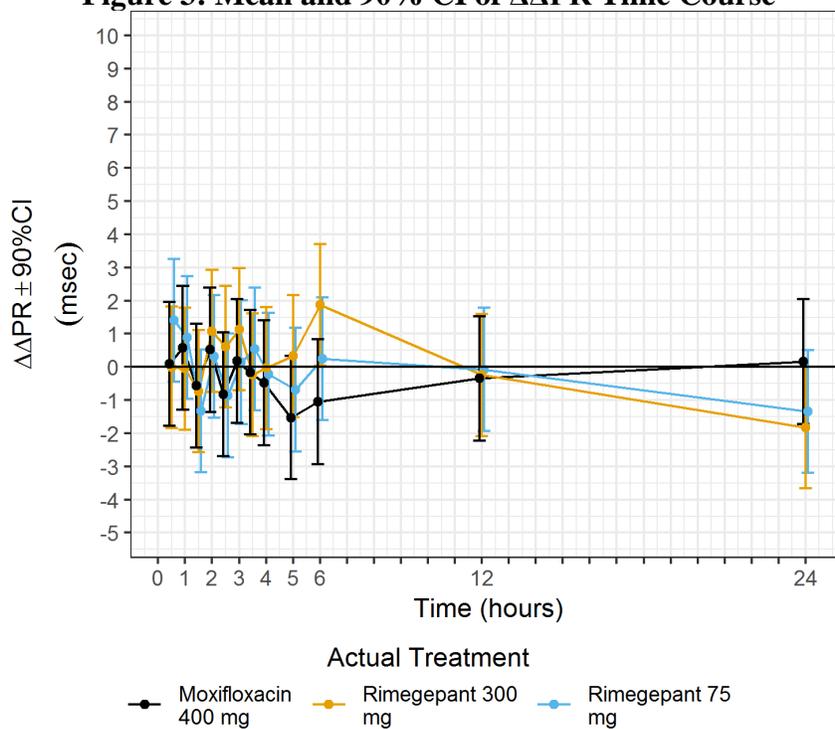


Table 5: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for $\Delta\Delta PR$

Treatment	Time (h)	$\Delta\Delta PR$ (ms)	90% CI (ms)
Rimegepant 75 mg	0.5	1.4	(-0.4 to 3.3)
Rimegepant 300 mg	6	1.9	(0.0 to 3.7)

4.3.4 QRS

Figure 4 displays the time profile of $\Delta\Delta QRS$ based on MMRM analysis. The $\Delta\Delta QRS$ values with the largest upper bounds by treatment are shown in Table 6.

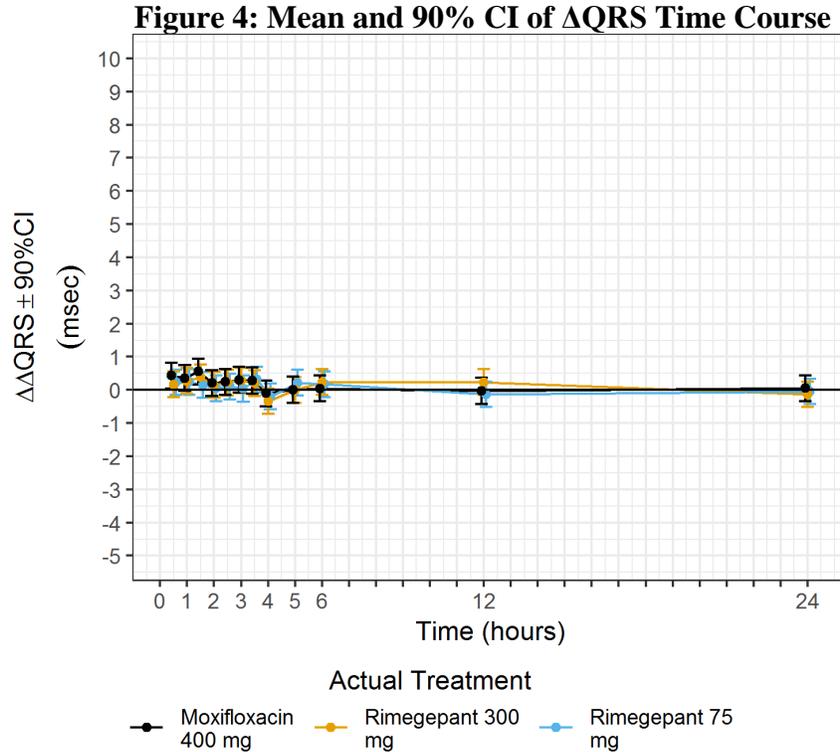


Table 6: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Δ QRS

Treatment	Time (h)	Δ QRS (ms)	90% CI (ms)
Rimegepant 75 mg	3.5	0.3	(-0.1 to 0.7)
Rimegepant 300 mg	1.5	0.4	(-0.0 to 0.8)

4.4 CATEGORICAL ANALYSIS

4.4.1 QTc

No subject had QTcF >450 ms or Δ QTcF >60 ms.

4.4.2 PR

No subject had PR >220 ms.

4.4.3 QRS

No subject had QRS >120 ms and more than 25 % increase from baseline.

4.4.4 HR

No subject had HR >100 bpm.

4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between drug concentration and Δ QTcF.

Prior to evaluating the relationship using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and ΔQTcF ; and 3) presence of non-linear relationship. An evaluation of the time-course of drug concentration and changes in ΔHR and ΔQTcF is shown in Figure 2 and Figure 5, respectively, which shows an absence of significant changes in HR and do not appear to show significant hysteresis. There is dose-dependent increase in drug exposure but not in QTc . Figure 6 shows the relationship between drug concentration and ΔQTcF and supports the use of a linear model.

Figure 5: Time Course of Drug Concentration (top) and QTcF (bottom)

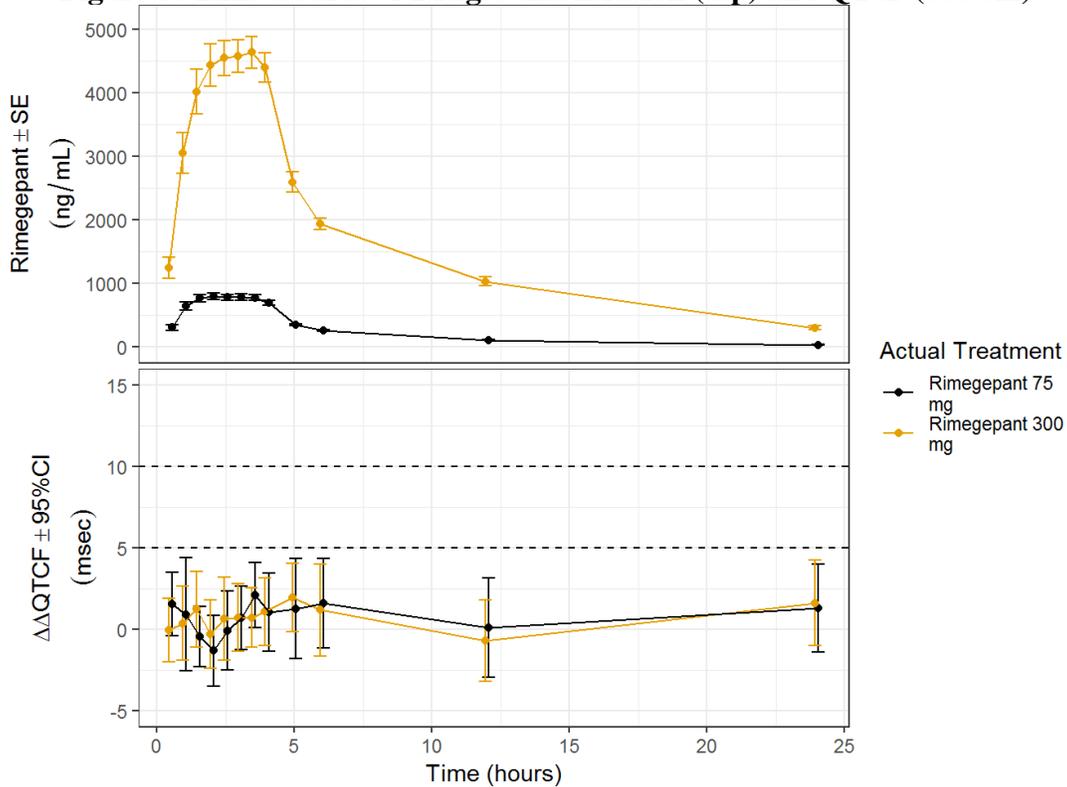
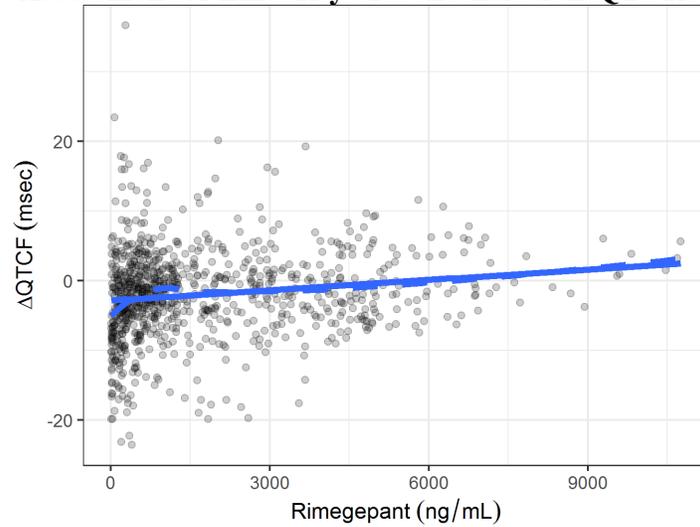
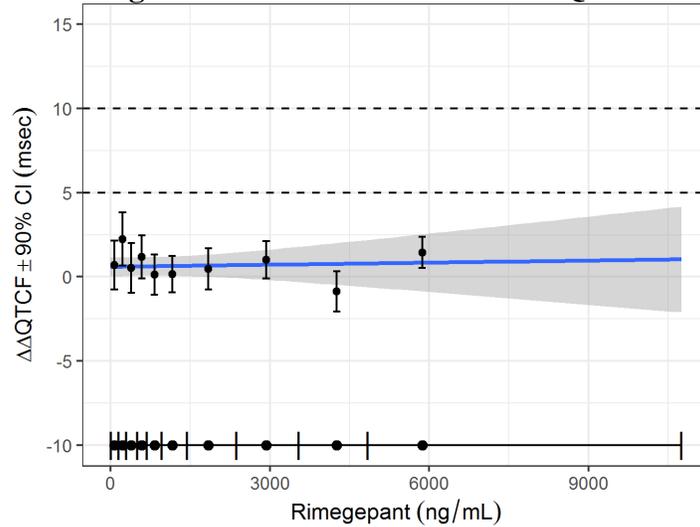


Figure 6: Assessment of Linearity of Concentration-QTc Relationship



Finally, the linear model ($\Delta QTcF \sim 1 + TRT + CONC + TIME + \text{adjusted_baseline}$, with random subject effect on the intercept and slope) was applied to the data and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTc model are provided in Table 1.

Figure 7: Goodness-of-fit Plot for QTc



4.5.1 Assay sensitivity

The PK profile of moxifloxacin are generally consistent with the ascending, peak and descending phase of historical data (Figure 8). When the same concentration-QTc model was applied on moxifloxacin data, the slope of the moxifloxacin concentration- ΔQTc relationship was statistically significant (0.005 msec per ng/mL, p -value<0.001). The predicted $\Delta \Delta QTcF$ interval at observed geometric C_{max} 1848 ng/mL of moxifloxacin was 13.8 msec (90% CI: 12.0 - 15.7 msec). Therefore, assay sensitivity was established.

Figure 8: Time Course of Moxifloxacin Concentration (top) and QTcF (bottom)

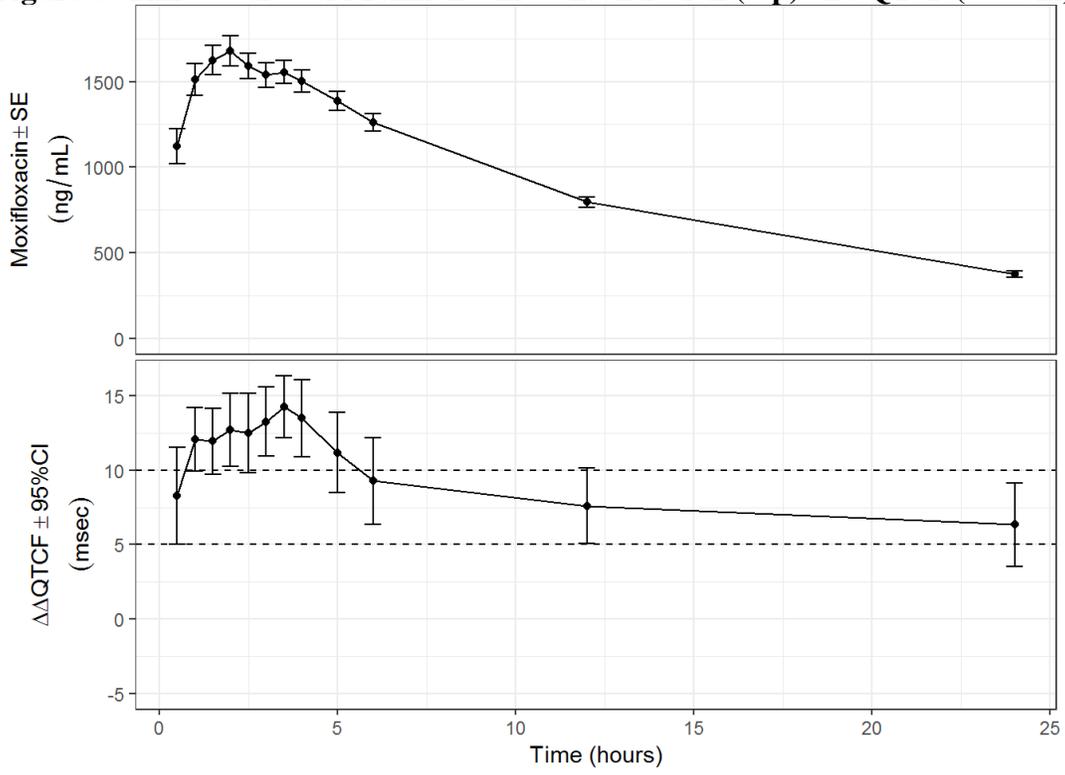
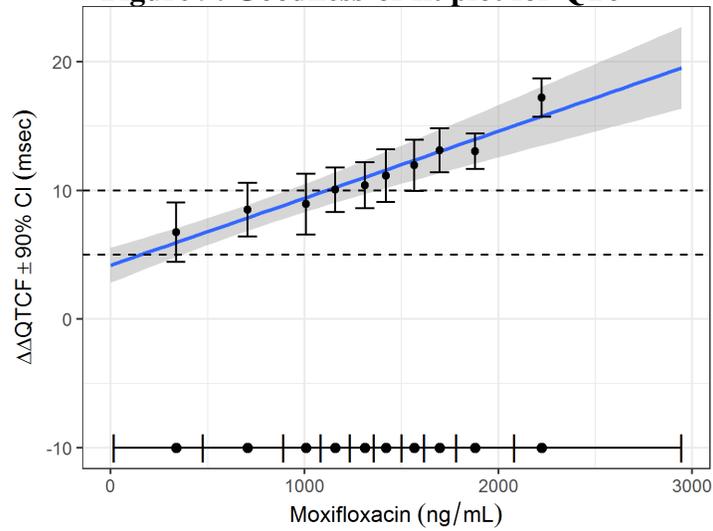


Figure 9: Goodness-of-fit plot for QTc



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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 29, 2019
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA (b) (4) NDA 212728 (orally disintegrating tablet)
Product Name and Strength:	rimegepant tablet, 75 mg rimegepant orally disintegrating tablet, 75 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Biohaven Pharmaceutical Holding Company Ltd
FDA Received Date:	June 27, 2019, June 28, 2019, and September 13, 2019
OSE RCM #:	2019-1380 and 2019-1377
DMEPA Safety Evaluator:	Celeste Karpow, PharmD, MPH
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 REASON FOR REVIEW

As part of the approval process for rimegepant tablets, NDA (b) (4) and rimegepant orally disintegrating tablets (ODT,) NDA 212728, the Division of Neurology Products (DNP) requested that we review the proposed rimegepant prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed Prescribing Information did not identify any medication safety concerns, at this time. However, our review of the proposed container label for rimegepant tablets and the proposed blister container label and carton labeling for rimegepant orally disintegrating tablets identified the following areas of needed improvement that may contribute to medication errors:

Container label for the (b) (4) Blister Carton labeling for 8-count ODT, and Professional Sample Blister Carton labeling 2-count ODT

- The placement of the graphic at the beginning of the proprietary name competes with the readability of the proprietary name, which may lead to misinterpretation of the proprietary name as "Ctradename."
- The first letter of the proprietary name is not capitalized which may lead to misinterpretation of the proprietary name.

- We note the strength is currently presented without a space between the numerical dose and the unit of measure which can negatively impact readability (e.g., the “m” can sometimes be mistaken as a zero or two zeros).
- We note the presentation of the proprietary name, established name, strength, and dosage form is not consistent with our guidance^a.
- If space permits, the format of the expiration date can be improved.

Blister Carton labeling for 8-count ODT (b) (4)

- It is not immediately clear that the designated strength (i.e., 75 mg) is per unit (one orally disintegrating tablet), which may lead to wrong dose errors.
- We note the net quantity statement appears more prominent than the established name, dosage form, and strength on the outer flap and the net quantity statement appears twice (e.g., (b) (4) “This package contains 8 TRADENAME ODT”). From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity is presented more prominently on the label than is the product strength^a. Per our guidance, the proprietary name, established name, product strength, route of administration, and warnings (if any) or cautionary statements (if any) should be the most prominent information on the PDP^a.
- The statement “Do not attempt to push the TRADENAME ODT through the foil backing” is written in negative language which is prone to misinterpretation if the word, “not” is overlooked.
- The dosage statement (b) (4) (b) (4), which may pose risk of wrong dose medication errors.
- The statement “(b) (4)” may lead to confusion because “(b) (4)” is not the correct terminology.

Professional Sample Blister Carton labeling 2-count ODT

(b) (4)

(b) (4)

(b) (4)

^a Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

4 CONCLUSION & RECOMMENDATIONS

We identified areas of the (b) (4) blister container label, blister carton labeling, and professional sample labeling where additional important information should be added to or revised in order to help ensure the safe use of the product. We provide recommendations below in section 4.1 to address our concerns and we advise these recommendations be implemented prior to the approval of these applications.

4.1 RECOMMENDATIONS FOR BIOHAVEN PHARMACEUTICAL HOLDING COMPANY LTD

We recommend the following be implemented prior to approval of NDA (b) (4) and NDA 212728:

- A. Container label for the (b) (4) Blister Carton labeling for 8-count ODT, and Professional Sample Blister Carton labeling 2-count ODT
 1. The placement of the graphic at the beginning of the proprietary name competes with the readability of the proprietary name, which may lead to misinterpretation of the proprietary name as “Ctradename.” Consider deleting, moving, and/or decreasing the prominence of the graphic at the beginning of the proprietary name.
 - a. The first letter of the proprietary name is not capitalized which may lead to misinterpretation of the proprietary name. Consider capitalizing the first letter of the proprietary name.
 2. The strength is currently presented without a space between the numerical dose and the unit of measure which can negatively impact readability (e.g., the “m” can sometimes be mistaken as a zero or two zeros). To improve readability, place adequate space between the numerical dose and unit of measure (e.g. 75 mg instead of 75mg).
 3. The presentation of the proprietary name, established name, strength, and dosage form is not consistent with our guidance^b. In addition, the established name is not in parentheses. We recommend you clearly separate the established name from the dosage form with parentheses. For example, you might consider:

^b Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

(b) (4) and “(rimegepant) orally disintegrating tablets”. See examples below:

(b) (4)	Tradename
(b) (4)	(rimegepant) orally disintegrating tablets
(b) (4)	75 mg per orally disintegrating tablet

4. As currently presented, the format for the expiration date is “YYYY-MM.” To minimize confusion and reduce the risk for deteriorated drug medication errors, FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day, if space permits. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

B. Blister Carton labeling for 8-count ODT (b) (4)

1. It is not immediately clear that the designated strength (i.e., 75 mg) is per unit (one orally disintegrating tablet), which may lead to wrong dose errors. Revise the strength statement (b) (4) to state “75 mg per orally disintegrating tablet” to make it clear that the designated strength is per unit^c.
2. The net quantity statement appears more prominent than the established name, dosage form, and strength on the outer flap and the net quantity statement appears twice (e.g., (b) (4) “This package contains 8 TRADENAME ODT”). From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity is presented more prominently on the label than is the product strength^c. Per our guidance, the proprietary name, established name, product strength, route of administration, and warnings (if any) or cautionary statements (if any) should be the most prominent information on the PDP^c. We recommend you revise the outer flap to list the net quantity once and ensure the prominence of the net quantity statement does not detract from the product strength, or other important information on the outer flap.
3. The statement “Do not attempt to push the TRADENAME ODT through the foil backing” uses negative language. Based on our post-marketing experience,

^c Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

negative statements (e.g. do not) may have the opposite of the intended meaning because the word “not” can be overlooked, and the warning may be misinterpreted as an affirmative action^d. We recommend the affirmative action “remove by gently peeling back the foil” precede the negative statement wherever it appears on the carton labeling. For example, consider revising the ‘usage’ statement to read: Store tablets in blister until ready to administer. With dry hands, peel back the foil backing of 1 blister and gently remove. Immediately place under or on top of the tongue where it will dissolve in seconds. Do not attempt to push the TRADENAME ODT through the foil backing.

4. The dosage statement (b) (4)
(b) (4)
To minimize the risk of wrong dose medication errors, revise the statement, (b) (4) to read “Recommended Dosage: See prescribing information”.
5. The statement (b) (4) may lead to confusion because (b) (4) is not the correct terminology. To ensure consistency with the physician labeling rule (PLR) formatted Prescribing Information, replace (b) (4) with “prescribing information”.

C. Professional Sample Blister Carton label 2-count ODT

(b) (4)

- D. (b) (4)
- (b) (4)

^d Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

^e Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

route of administration, and warnings (if any) or cautionary statements (if any) are the most prominent information on the PDP^f.

2. It is unclear whether the linear barcode is surrounded by sufficient white space to allow scanners to correctly read the barcode. Ensure the linear barcode is surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).

^f Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for rimegepant received on June 27, 2019 and June 28, 2019 from Biohaven Pharmaceutical Holding Company Ltd.

Table 2. Relevant Product Information for rimegepant		
Product Name	rimegepant	Rimegepant ODT
Active Ingredient	rimegepant	
Indication	acute treatment of migraine in adults.	
Route of Administration	oral	
Dosage Form	tablet	Orally disintegrating tablet
Strength	75 mg	
Dose and Frequency	75 mg, as needed (b) (4) for the acute treatment of migraine. (b) (4)	
How Supplied	bottle containing 30 tablets	cartons containing a blister pack of 8 orally disintegrating tablets
Storage	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].	
Container Closure	(b) (4)	PVC adhered to foil

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 18, 2019, we searched for previous DMEPA reviews relevant to this current review using the term, "rimegepant." Our search did not identify any previous reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^g along with postmarket medication error data, we reviewed the following rimegepant labels and labeling submitted by Biohaven Pharmaceutical Holding Company Ltd.

- Container label for the [REDACTED]^{(b) (4)} received on June 28, 2019
- Blister Carton labeling for 8-count ODT received on June 27, 2019
- Blister Container label for ODT received on June 27, 2019
- Professional Sample Blister Carton labeling 2-count ODT received on June 27, 2019
- Prescribing Information (Image not shown) received on September 13, 2019

G.2 Label and Labeling Images



13 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

^g Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/

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