CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216386Orig1s000

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 Memo

Date:	March 9, 2023
Reviewer:	Danielle Abraham, PhD, MPH Division of Epidemiology I
Team Leader:	Kira Leishear White, PhD, MS Division of Epidemiology I
Division Director:	CAPT Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	Zavzpret (zavegepant)
Application Type/Number:	NDA 216386
Applicant/sponsor:	Pfizer Inc
OSE RCM #:	2022-1034 (TTT)

This is a corrected memo that does not change the overall recommendations/conclusions of the original memo dated March 8, 2023.

1. BACKGROUND INFORMATION

1.1. Medical Product

Zavegepant (Zavzpret, Pfizer Inc) nasal spray is a small molecule, calcitonin gene-related peptide (CGRP) receptor antagonist.[1] The proposed indication for this new drug application (NDA) is for the acute treatment of migraine with or without aura in adults.[2]

CGRP and CGRP receptors are found throughout both the central and peripheral nervous system (1, 2). CGRP has a role in several physiologic processes, including vasodilation (1, 2). CGRP is thought to be involved in migraine etiology (1, 2). Other drugs in the same class, with an oral route of administration, are currently approved for the acute treatment of migraine with or without aura in adults (ubrogepant[3]), the preventive treatment of episodic migraine in adults (atogepant[4]), and both the acute treatment of migraine with or without aura in adults and the preventive treatment of episodic migraine in adults (rimegepant[5]).

The recommended dose of zavegepant is 10 mg given as a single spray in one nostril, as needed.[6] The maximum dose in a 24-hour period is 10 mg; the safety of treating more than eight migraines in a 30-day period has not been established.[7] The effective half-life of zavegepant after a 10 mg dose of the nasal spray is 6.55 hours.[8] Per the March 7, 2023, draft labeling, warnings and precautions for zavegepant include hypersensitivity reactions.[9] Adverse reactions reported in at least 2% of patients treated with zavegepant (and greater than placebo) included taste disorders, nausea, nasal discomfort, and vomiting.[10]

1.2. Describe the Safety Concern

The Division of Neurology 2 (DN2) requested that the Division of Epidemiology I (DEPI-I) assess the sufficiency of Active Risk Identification and Analysis (ARIA) to evaluate the safety of zavegepant exposure during pregnancy.

The prevalence of migraine differs by age and sex (3, 4). The prevalence of migraine is higher among females, compared to males (3, 4). In one U.S. study, the one-year prevalence of migraine among females by age group was highest among those 30-39 years of age (28.1%)

[1] Draft ZAVZPRET labeling dated March 7, 2023.; Kau R. NDA 216386 Zavzpret (zavegepant). Clinical Review. March 9, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Ref ID: 5138696.
[2] Draft ZAVZPRET labeling dated March 7, 2023.
[3] NDA 211765 Label. February 17, 2023. Silver Spring (MD), U.S. Food and Drug Administration. Accessed on March 7, 2023, at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/211765s007lbl.pdf.
[4] NDA 215206 Label. September 28, 2021. Silver Spring (MD), U.S. Food and Drug Administration. Accessed on March 7, 2023, at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215206Orig1s000lbl.pdf.
[5] NDA 212728 Label. April 11, 2022. Silver Spring (MD), U.S. Food and Drug Administration. Accessed on March 7, 2023, at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/212728s009lbl.pdf.
[6] See footnote 2.
[7] Ibid.
[8] Ibid.
[9] Ibid.
[10] Ibid.

(3). Prevalence was also greater than 20% in those 40-49 years of age (25.5%) and those 18-29 years of age (20.4%) (3). Global data suggest that migraine prevalence is the highest between 35 and 39 years of age (4). Consequently, the prevalence of migraine is highest among females during childbearing years, thus there is the potential for migraine treatment exposure in this population.

Migraine symptoms may improve during pregnancy (5). However, there is some evidence that migraine may impact some pregnancy outcomes, particularly pregnancy-induced hypertension disorders and preeclampsia/eclampsia (5, 6).

Non-clinical studies found no adverse effects of zavegepant on development. There were no effects of subcutaneous administration of zavegepant to pregnant rats (0, 10, 20, or 40 mg/kg/day) and pregnant rabbits (0, 20, 40, or 60 mg/kg/day) during organogenesis on embryofetal development. Subcutaneous administration of zavegepant (0, 5, 10, or 20 mg/kg/day) in rats throughout pregnancy and lactation resulted in no adverse effects on pre- and postnatal development.[11]

There are limited data on the safety associated with the use of zavegepant in pregnant women.[12] The clinical development program excluded females who were pregnant, lactating, or unwilling/unable to use an effective contraceptive method.[13] Based on the summary of clinical safety[14] and the 120-day safety update,[15] there were 13 pregnancies among patients who received at least one dose of zavegepant, although three later had subsequent negative pregnancy tests after positive tests.[16] Three pregnancies were not considered exposed as they did not meet the definition of zavegepant exposure based on five half-lives prior to the estimated date of conception (last menstrual period+14 days) or during pregnancy.[17] Among the remaining seven pregnancies with zavegepant exposure, three ended in live, full-term births without congenital anomalies or pregnancy complications.[18] One pregnancy[19] ended in a live, full-term birth without congenital anomalies or pregnancy complications with subsequent neonatal death at a calculated age of two weeks. The suspected cause of death was sudden infant death syndrome. Three pregnancies ended in voluntary terminations for unknown reasons (gestational ages for each: 5 weeks, 5 weeks, 8 weeks).

The proposed, March 7, 2023, draft labeling for zavegepant includes the following language about use in specific populations:[20]

8 USE IN SPECIFIC POPULATIONS

[11] Draft ZAVZPRET labeling dated March 7, 2023.
[12] Ibid.
[13] Kau R. NDA 216386 Zavzpret (zavegepant). Clinical Review. March 9, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Ref ID: 5138696.
[14] Biohaven pharmaceuticals. Summary of Clinical Safety. Zavegepant. February 21, 2022.
[15] Biohaven pharmaceuticals. 120-day Safety Update Report. Zavegepant. June 24, 2022.
[16] See footnote 13.
[17] See footnote 14.
[18] Includes one pregnancy that was listed as ongoing in the Summary of Clinical Safety that, according to the 120-day Safety Update Report, resulted in a live, full-term birth.
[19] Subject received only one dose of zavegepant during the first trimester.
[20] See footnote 11.

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of ZAVZPRET in pregnant women. No adverse developmental effects were observed following subcutaneous administration of zavegepant to pregnant animals at doses associated with plasma exposures higher than those used clinically (see Data).

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

Subcutaneous administration of zavegepant to pregnant rats (0, 10, 20, or 40 mg/kg/day) or rabbits (0, 20, 40, or 60 mg/kg/day) during the period of organogenesis resulted in no adverse effects on embryofetal development. Plasma exposures (AUC) at the highest doses tested are approximately 4000 times that in humans at the maximum recommended human dose (MRHD) of 10 mg/day.

Subcutaneous administration of zavegepant (0, 5, 10, or 20 mg/kg/day) to rats throughout pregnancy and lactation resulted in no adverse effects on pre- and postnatal development. Plasma exposure (AUC) at the highest doses tested was approximately 2500 times that in humans at the MRHD.

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 with outcome validation 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:

Outcomes: ARIA lacks access to medical records. The pregnancy registry being considered requires that an expert clinical geneticist or dysmorphologist review and classify medical records of all major congenital malformations. Also, although in a first stage, the study using claims or electronic medical data may be algorithm-based, if it shows an imbalance in any of the outcomes being investigated, FDA will require outcome validation in the selected database(s) or a chart-confirmed analysis.

Analytical tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been fully tested and implemented in postmarketing surveillance of maternal and fetal outcomes. The ARIA analytic tools that assess drug use in pregnancy (and maternal and neonatal outcomes) currently include only women with a live-birth delivery.

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

The draft language, as of February 7, 2023, for the conduct of two pregnancy outcomes PMRs are as follows:

- PMR 4408-5: Prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with migraine exposed to zavegepant during pregnancy with two unexposed control populations: one consisting of women with migraine who have not been exposed to zavegepant 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 4408-6: A pregnancy outcomes study using a different study design than provided for in PMR 4408-5 above (for example, a retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study) to assess pregnancy complications, major congenital malformations, spontaneous abortions, stillbirths, and small-for-gestational-age births in women exposed to zavegepant during pregnancy compared to an unexposed control population.

REFERENCES

1. Edvinsson L, Warfvinge K. Recognizing the role of CGRP and CGRP receptors in migraine and its treatment. Cephalalgia. 2019;39(3):366-73.
2. Charles A, Pozo-Rosich P. Targeting calcitonin gene-related peptide: a new era in migraine therapy. Lancet. 2019 Nov 9;394(10210):1765-74.
3. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007 Jan 30;68(5):343-9.
4. GBD 2016 Headache Collaborators. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018 Nov;17(11):954-76.
5. MacGregor EA. Headache in pregnancy. Neurol Clin. 2012 Aug;30(3):835-66.
6. Skajaa N, Szépligeti SK, Xue F, Sørensen HT, Ehrenstein V, Eisele O, et al. Pregnancy, birth, neonatal, and postnatal neurological outcomes after pregnancy with migraine. Headache. 2019 Jun;59(6):869-79.

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/

DANIELLE S ABRAHAM
03/09/2023 12:19:51 PM

KIRA N LEISHEAR WHITE
03/09/2023 12:21:27 PM

SUKHMINDER K SANDHU
03/09/2023 12:22:24 PM

JUDITH W ZANDER
03/09/2023 12:23:18 PM

PATRICIA L BRIGHT
03/09/2023 12:26:04 PM

ROBERT BALL
03/09/2023 12:26:54 PM

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 21, 2023
To:	Lana Chen Senior Regulatory 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)** Sapna Shah, PharmD **Regulatory Review Officer** **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	ZAVZPRET (zavegepant)
Dosage Form and Route:	nasal spray
Application Type/Number:	NDA 216386
Applicant:	BioHaven Pharmaceuticals Inc.

1 INTRODUCTION

On March 9, 2022, BioHaven Pharmacueticals, Inc. submitted for the Agency's review an original 505(b)(1) New Drug Application (NDA) 216386 for ZAVZPRET (zavegepant) nasal spray, for intranasal use. The Applicant is seeking FDA approval for prescription marketing of the drug product for the treatment of adults with acute migraine with or without aura.

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 May 4, 2022, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for ZAVZPRET (zavegepant) nasal spray.

2 MATERIAL REVIEWED

- Draft ZAVZPRET (zavegepant) nasal spray PPI and IFU received on March 9, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 8, 2023.
- Draft ZAVZPRET (zavegepant) nasal spray Prescribing Information (PI) received on March 9, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 8, 2023.

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.

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.

In our collaborative review of the PPI and IFU we:

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

4 CONCLUSIONS

The PPI and IFU are 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 and IFU are 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 and IFU.

Please let us know if you have any questions.

16 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

---

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/

KELLY D JACKSON
02/21/2023 08:59:29 AM

MARCIA B WILLIAMS
02/21/2023 09:02:43 AM

SAPNA SHAH
02/21/2023 09:05:20 AM

LASHAWN M GRIFFITHS
02/21/2023 09:10:43 AM

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

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

Memorandum

Date: February 17, 2023

To: Lana Chen, Regulatory Project Manager, Division of Neurology 2 (DN2)

Heather Fitter, Cross Disciplinary Team Leader, DN2

Tracy Peters, Associate Director for Labeling, DN2

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

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for ZAVZPRET™ (zavegepant) nasal spray

NDA: 216386

Background:
In response to DN2's consult request dated May 4, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for ZAVZPRET™ (zavegepant) nasal spray (Zavzpret).

PI/PPI /IFU:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP from DN2 (Lana Chen) on February 8, 2023, and our comments are provided below.

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

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on December 7, 2022 and February 1, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Sapna Shah at 240-402-6068 or Sapna.Shah@fda.hhs.gov.

22 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

---

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/

SAPNA SHAH
02/17/2023 01:50:29 PM

Division of Hepatology and Nutrition Consultation

Drug-induced Liver Injury Team

NDA	216386
Consultation Issue	Drug-induced liver injury (DILI)
Drug Product	Zavegepant
Indication	Migraine
Applicant	Biohaven
Requesting Division	Division of Neurology 2 (DN2)
Primary Reviewer	Ling Lan, MD, PhD, Clinical Analysist, DILI Team, DHN
Non-clinical Reviewer	Edwige ChiogoVouffo, PharmD, PhD, DILI Team, DHN
Secondary Reviewer	Paul H. Hayashi, MD, MPH DILI Team Lead, OND/DHN
Reviewer **Office of Pharmacoepidemiology**	Mark Avigan, MD, CM Associate Director, OPE/OSE
Signatory Authority	Frank Anania, MD Acting Director, OND/DHN
Assessment Date	Feb 9, 2023

Context: Zavegepant (ZGNT) is a small molecule, calcitonin gene related peptide receptor antagonist (CGRP-ra) delivered intranasally for the treatment of migraine headaches. Two of the first CGRP-ra's developed had significant hepatotoxicity issues and were abandoned in development, but three CGRP-ra's have been approved for migraines since 2019. Cases of elevated aminotransferases were seen in the ZGNT pivotal and safety trials. The Division of Neurology 2 (DN2) requested the DILI Team provide opinion on these cases and the DILI risk with intranasal ZGNT.

Executive Summary: We do not see a significant DILI risk with intranasal ZGNT that would hold up approval, require significant labeling, or require post-market research studies. We assessed 84% of the liver injury cases as unlikely ZGNT-related liver injury. The remaining cases of probable or possible DILI due to ZGNT were associated with mild injuries without hyperbilirubinemia, and thus there were no Hy's Law cases. There were no clear imbalances in liver enzyme elevations between treatment and comparator arms. However, the randomized control data were limited to single dose studies. There were modest aminotransaminase elevations possibly attributable to ZGNT in the repeated dose safety trial. Thus, intranasal (IN) ZGNT can cause mild to modest elevation in aminotransferases; if there is a propensity for patients to use the IN ZGNT substantially more often than prescribed, significant liver injury could arise post-market. However, at the dosing used in the clinical trials, the risk of clinically apparent DILI seems low.

Consultation Sections:

Section 1.0 – Target Disease and Rationale
Section 2.0 - ADME pertinent to DILI
Section 3.0 - Non-clinical data pertinent to DILI.
Section 4.0 - Clinical data
Section 5.0 – Assessment & Recommendations.
Appendix: Trial schematics

Abbreviations:
ALP: alkaline phosphatase
ALT: alanine aminotransferase
AP: alkaline phosphatase
AST: aspartate aminotransferase
BHV-3500: ZGNT or zavegepant
BMI: body mass index
CGRP: calcitonin gene related peptide
CGRP-ra: CGRP receptor antagonist
CK: creatinine phosphokinase
CYP: cytochrome P450
DB: direct bilirubin
DILI: drug-induced liver injury
GGT: gamma-glutamyl transferase
HDS: herbal and dietary supplements
IN: intranasal
IP: investigational product
IV: intravenous
LDH: lactate dehydrogenase
PRN: pre re nata
R-value: ALT/ULN ÷ ALP/ULN
SC: subcutaneous
TB: total bilirubin
US: ultrasound
ULN: upper limit of normal
ZGNT: zavegepant or BHV3500

1.0 Target Disease and Rationale

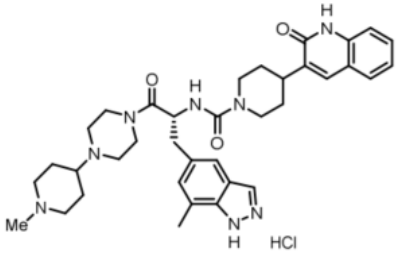
Please see the DILI Team's consult note for rimegepant, IND 109886, logged in DARRTS on Jan 30, 2023.[1] The targeted disease and rationale for use of rimegepant and zavegepant in migraines are the same. Both drugs are calcitonin gene related peptide, receptor antagonists (CGRP-ra).

2.0 ADME data pertinent to DILI

2.1 Structure: ZGNT structure is shown in **Figure 1**.

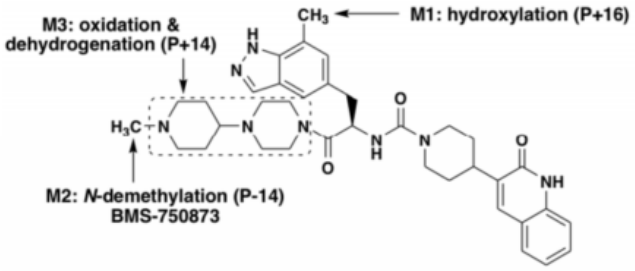
[1] Open DARRTS session first to enable following link to work:
https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806ae16a

Figure 1: Molecular structure zavegepant (BHV 3500)[2]



2.2 Absorption: Zavegepant (ZGNT) showed a dose-dependent and rapid intranasal (IN) absorption (Tmax= 0.25 to 0.56 hrs) even at low doses in rabbits. ZGNT IN bioavailability is dose dependent. It showed a mean bioavailability of 13% (10 mg/mL), 19% (30 mg/mL), and 30% (100 mg/mL) in rabbits. The subcutaneous (SC) bioavailability was high in rats (87%) and in monkeys (85%), in dogs (117%), and in marmoset (115%). Hence, the SC bioavailability was higher than the IN bioavailability, but rapid nasal absorption was observed.
2.3 Distribution: In vitro protein binding study of BHV-3500 showed a relatively high free-fraction (26 to 51%) in human, rat, dog, monkey, and marmoset. ZGNT was widely and well distributed following intravenous (IV) administration in rats. It declined quickly from the systemic circulation. Thus, ZGNT was well distributed with a high free fraction.
2.4 Metabolism: ZGNT circulated primarily as unchanged parent drug in rats and monkeys and had a very low rate of hepatic metabolism in all species. CYP3A4 is the major metabolizing CYP with CY2D6 as a minor CYP. Only 3 metabolites were identified across species. The test article was metabolized via oxidative pathways based on in vitro studies. The biotransformation pathways for ZGNT in monkeys are shown in **Figure 2.**

Figure 2: Biotransformation of ZGNT in vitro [3]



2.5 Elimination: Renal and biliary elimination of ZGNT parent compound are seen in rats after IV administration. It was eliminated unchanged over a nine-day period. Following an IV or SC administration, the major route of elimination was feces (65%), with urine (25%) being minor in monkeys. Thus, feces is the dominant elimination pathway.
2.6 Transport inhibition: BHV-3500 inhibited OATP1B1, OATP1B3, OCT1, MATE1, and MATEK2-K with IC50 of 43.1, 49.9, 2.15, and 0.158, and 4.96 µM respectively. BHV-3500 is a subtract for P-gp, MATE1 and MATE2-K, but not a subtract of BSEP, MRP2,

[2] NDA216386 (216386 - 0034 - (34) - 2023-02-01 - ORIG-1 /Labeling/Container-Carton Draft) - Structure
[3] NDA216386 (216386 - 0011 - (11) - 2022-08-19 - ORIG-1 /Quality/Response To Information Request) - Pharmacokinetics Written Summary-Initial (#18)

MRP3, and MRP4 (ABC) transporters. Accordingly, ZGNT is not predicted to cause bile acid accumulation that might increase the risk of DILI.

3.0 Non-clinical data:

3.1 In vitro data: ZGNT showed no inhibition of recombinant CYP1A2, 2C9, 2C19, and 2D6. It was the weak inhibitor of the recombinant CYP3A4 but without time or metabolism dependent inhibition. There was little to no induction of CYP1A2, CYP2B6, or CYP3A4 as measured by mRNA expression. However, it is 60% protein-bound in human hepatocytes. ZGNT showed poor intrinsic membrane permeability. Hence, there is no significant CYP-mediated drug-interaction because the ZGNT had only weak inhibition of one CYP (CYP3A4).

3.2 Animal Data: The NOAEL for the four-week study in mice was 2.5 mg/day with safety margin of 13x to 25x based on AUC when compared to 10 mg dose in humans. Following 28-day IN deliver to rats, there were slight accumulation of ZGNT based on C_{max} and AUC.

3.2.1 *Liver injury marker data*: Following a 28-day SC delivery, there were slight increases in transaminases at the higher dose of 37.5 mg/kg/day in monkeys and 25 mg/kg/day in rats. However, similar increases were also noted in the control group. ZGNT led to no mortality, liver-related biochemistry changes, or liver histopathology at single-doses of 1000, 3000, or 6000 mg/kg in female rats. There were elevations of transaminases (AST: 4.9x baseline; ALT: 2.4x baseline) in single SC dosing of monkeys without dose response relationship. There were slight increases in aminotransaminases after 28 days of SC ZGNT, 25 mg/kg/day in monkeys. The sponsor attributed the elevations to inflammation at the injection site. The NOAEL was 25 mg/kg/day. There were increases in aminotransaminases and AP in rats given 13-weeks of SC ZGNT at twelve mg/kg/da. There were slight aminotransaminase increases in monkeys after 28 days of SC ZGNT, 37.5 mg/kg/day, but no adverse changes after four, 13, and 26-weeks of IN delivery. Thus, mild increases in liver biochemistries occurred following single and repeated dosing.

3.2.2 *Liver Histopathology*: ZGNT caused minimal periportal hepatocellular vacuolation after 13 weeks of SC administration in rats at 12 mg/kg/day. There were no changes in liver weights or hepatocellular degeneration. There was minimal vacuolation and inflammation on liver histology after 28 day and 13 weeks of SC ZGNT exposure in monkeys. Thus, liver histologic changes were mild across 13 weeks of SC ZGNT deliver in rats and monkeys.

ADME and Toxicology Summary Tables

Table 1: ADME Summary as pertains to DILI risk[4]

Item	Finding
Absorption	Dose-dependent and rapid nasal absorption
Distribution	Well distributed, high free fraction noted in all studied species.
Metabolism	CYP3A4 primarily; Most circulates as unchanged parent drug. Three metabolites identified.
Elimination	Eliminated unchanged with the pathways being feces (65%) and urine (25%)

[4] Table made by DILI Team

Table 2: Toxicology summary as pertains to DILI risk[5]

Item	Finding
In Vitro Studies	
Major CYPs	Major CYPs: recombinant CYP3A4 with minor one be recombinant CY2D6; no time dependent inhibition
Reaction metabolites (i.e., glutathione trapping)	No data found
Mitochondria studies/inhibition	No data found
Transporter (BSEP or MRP2 inhibition)	Not a substrate for BSEP or MRP2
Animal Studies	
Elevation in liver analytes (e.g., ALT, AP, TB)	Mild increases in liver markers were noted
Liver histopathology findings (animal species)	Minimal hepatocellular vacuolation and minimal inflammation of the liver noted

Overall non-clinical summary: In vitro studies do not suggest significant DILI risk, though we found no studies on metabolite formation (e.g., glutathione trapping) or mitochondrial effects. Animal studies suggest ZGNT is well tolerated. Some mild changes were observed in liver biochemistries and liver histology with long term IV and SC toxicity studies. IN administration show non-adverse changes for up to 26 weeks of exposure.

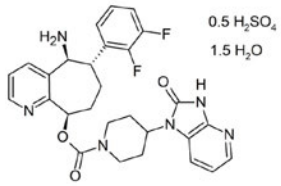
4.0 Clinical Data

4.1 In class or near class data on DILI: Telcagepant was one of the first CGRP receptor antagonist (CGRP-ra), but its development was stopped due to liver injury seen in phase 3 studies, primarily when given daily for more than seven days.[6] Similarly, development of MK-3207 was also halted due to liver injury concerns in early development. The mechanism of liver injury for these agents was postulated to be a combination of bile acid accumulation (transport inhibition), oxidative stress (reactive metabolite formation), and mitochondrial toxicity. In vitro and in silico testing have led to the development of other CGRP receptor antagonists with less hepatotoxicity.[7] Since abandonment of telcagepant and MK-3207, the FDA approved three CGRP-ra's for treatment or prevention of acute migraine; There were no significant liver injury concerns. (**Figure 3** and **Table 3**) The DILI Team provided consultations for atogepant pre-market[8] and rimegepant post-market;[9] we considered the risk of clinically significant DILI for both drugs to be low. A PubMed search did not find case reports of liver injury due to the three marketed agents (search terms: "liver injury", "hepatotoxicity", and "DILI") though approvals are relatively recent (2019 to 2021).

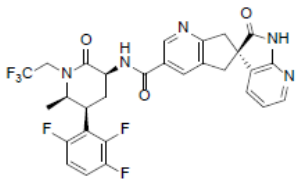
[5] Table made by DILI Team
[6] Holland PR, et al. Targeted CGRP Small Molecule Antagonists for Acute Migraine Therapy. *Neurotherapeutics* 2018; 15:304-312 DOI: https://doi.org/10.1007/s13311-018-0617-4
[7] Smith, B, et al. Mechanistic Investigations Support Liver Safety of Ubrogepant. *Toxicological Sciences*, 2020; 177:84-93. DOI: https://doi.org/10.1093/toxsci/kfaa093
[8] Open DARRTS session first to enable following link to work: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8061050a
[9] Open DARRTS session first to enable following link to work: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806ae16a

Figure 3: Structural formulas for rimegepant, atogepant, ubrogepant and zavegepant[10],[11],[12],[13]

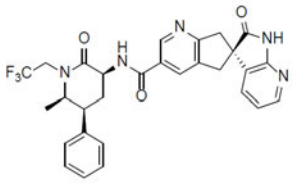
rimegepant



atogepant



ubrogepant



zavegepant

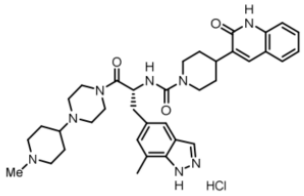


Table 3: Approved oral, small molecule, CRGP receptor antagonists and DILI risk[14]

Drug	Indication	Approval year	Package insert	LiverTox® risk category
Atogepant	Prevent migraine	2021	No mention of significant DILI risk	Not yet entered in LiverTox
Rimegepant	Acute migraine	2020	No mention of significant DILI risk	E: unlikely cause of clinically apparent acute liver injury[15]
Ubrogepant	Acute migraine	2019	No mention of significant DILI risk	E: unlikely cause of clinically apparent acute liver injury[16]

FDA also approved four monoclonal antibody, CGRP antagonists: Eptinezumab (intravenous), Galcanezumab (subcutaneous, SC), Fremanezumab (SC), Erenumab (SC). There are no case reports of DILI from these agents in PubMed, and LiverTox® likelihood category is E for each, similar to the oral, small molecule CGRP-ra's listed in **Table 3** above. Thus, liver injury is unlikely to result from an on-target, downstream effect of blocking the CGRP receptor.

4.2 Clinical study analysis:

4.2.1: *Clinical studies and enrollment*: Four studies were assessed by the DILI Team. Randomized control data came from the two pivotal, placebo-controlled studies: Phase 3 study BHV3500-301 and Phase 2/3 study BHV3500-201. Administration of ZGNT for these two studies was intranasal (IN) and one dose only. There were 629 and 1185 subjects randomized to ZGNT in studies BHV3500-301 and BHV3500-201, respectively. (**Table 4**)

[10] https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212728s000lbl.pdf
[11] https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215206Orig1s000lbl.pdf
[12] https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211765s000lbl.pdf
[13] NDA216386 (216386 - 0034 - (34) - 2023-02-01 - ORIG-1 /Labeling/Container-Carton Draft) - Structure
[14] Table made by DILI Team
[15] LiverTox® https://www.ncbi.nlm.nih.gov/books/NBK572432/
[16] LiverTox® https://www.ncbi.nlm.nih.gov/books/NBK572431/

Table 4: Two pivotal studies with number of subjects enrolled.[17]

Study No. Status	Study Description	Dosing	Treatment Groups	No. of Subjects Treated/Evaluable*	Co-primary Endpoints
Phase 3 Clinical Study					
BHV3500-301[25] Pivotal Study Completed CSR available FPFV: 27-Oct-2020 LPLV: 22-Oct-2021	Double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of zavegepant 10 mg for the acute treatment of a single moderate to severe migraine	Single dose/ Aptar UDS/ Administered IN	Zavegepant 10 mg Placebo	1,282/1,269 629/623 653/646	(1) Pain freedom at 2 hours postdose (2) MBS freedom at 2 hours postdose
Phase 2/3 Clinical Study					
BHV3500-201[23] Pivotal Study Completed CSR available FPFV: 25-Mar-2019 LPLV: 11-Nov-2019	Double-blind, randomized, placebo-controlled, dose-ranging study to evaluate the efficacy and safety of zavegepant for the acute treatment of a single moderate to severe migraine	Single dose/ Aptar UDS/ Administered IN	Zavegepant 5 mg Zavegepant 10 mg Zavegepant 20 mg Placebo	1,588/1,581 388/387 394/391 403/402 403/401	(1) Pain freedom at 2 hours postdose (2) MBS freedom at 2 hours postdose

*Subjects were evaluable for efficacy (i.e, in the efficacy analysis set) if they were randomized only once, took study medication, had a migraine of moderate to severe intensity at the time of dosing, and had postdose efficacy data.
Abbreviations: CSR = clinical study report; FPFV = first patient first visit; IN = intranasal; LPLV = last patient last visit; MBS = most bothersome symptom; UDS = unit dose system

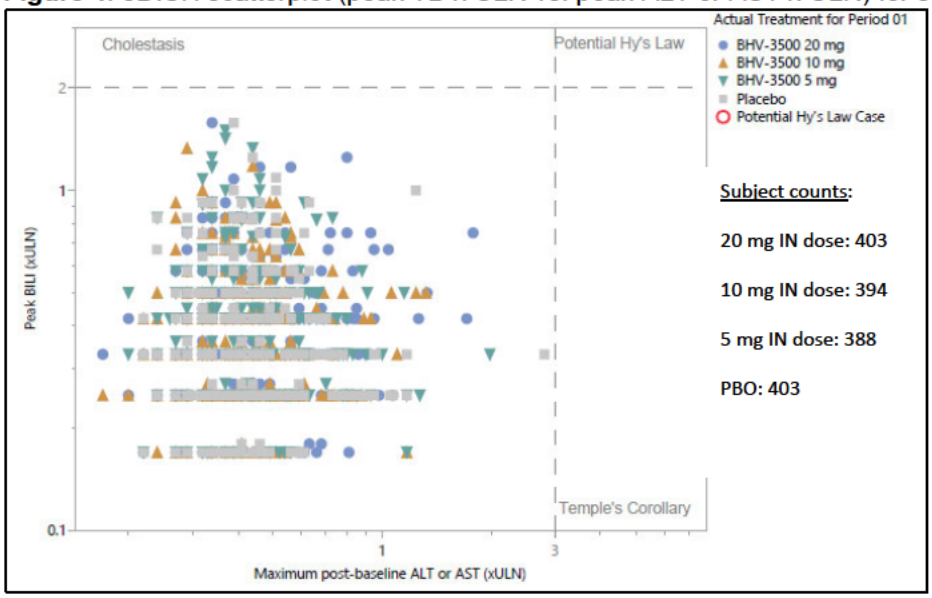
The third study was an open-label, long-term, safety trial using intranasal (IN) ZGNT (study BHV3500-202) that had 600 subjects exposed. In this study, subjects took IN ZGNT as needed for migraines and could take one 10 mg dose per day, to a maximum of eight days per 28 days. Dosing could span up to 52 weeks. Lastly, the DILI Team assessed one phase 1 study, Study BHV3500-106, an open-label, 8-week safety study of oral ZGNT in healthy volunteers. A total 364 healthy subjects were exposed to ZGNT. Schematics for the four studies are in the **Appendix**.

4.2.1 Enzyme and bilirubin changes across the four studies: Overall, there were few cases falling into Temple's Corollary quadrant and no cases in the Hy's law quadrants. For the randomized control trials (BHV3500-201 and BHV3500-301), there were no remarkable imbalances in liver enzyme or bilirubin changes.

4.2.1.1 **BHV3500-201**: This pivotal phase 2/3 study had no cases falling outside the left lower quadrant of the eDISH scatter plot across the three, single IN doses of 5, 10 and 20 mg. (**Figure 4**) Similarly, no subject was outside the left lower quadrant on the peak TB versus peak AP scatterplot (figure not shown).

[17] NDA216386 (216386 - 0011 - (11) - 2022-08-19 - ORIG-1 /Quality/Response To Information Request) - Clinical Overview-Initial (#24)

Figure 4: eDISH scatterplot (peak TB x ULN vs. peak ALT or AST x ULN) for study BHV3500-201[18]



4.2.1.2 BHV3500-301: This pivotal phase 3 study had just one subject on ZGNT fall outside the left lower quadrant and no subjects with TB >2 x ULN. (**Figure 5**) The subject (b) (6) in Temples Corollary is discussed in detail in section 4.3. The TB versus AP scatterplot had two subjects in the right lower quadrant, both of which were not considered DILI, and no subjects had TB > 2x ULN (Figure not shown).

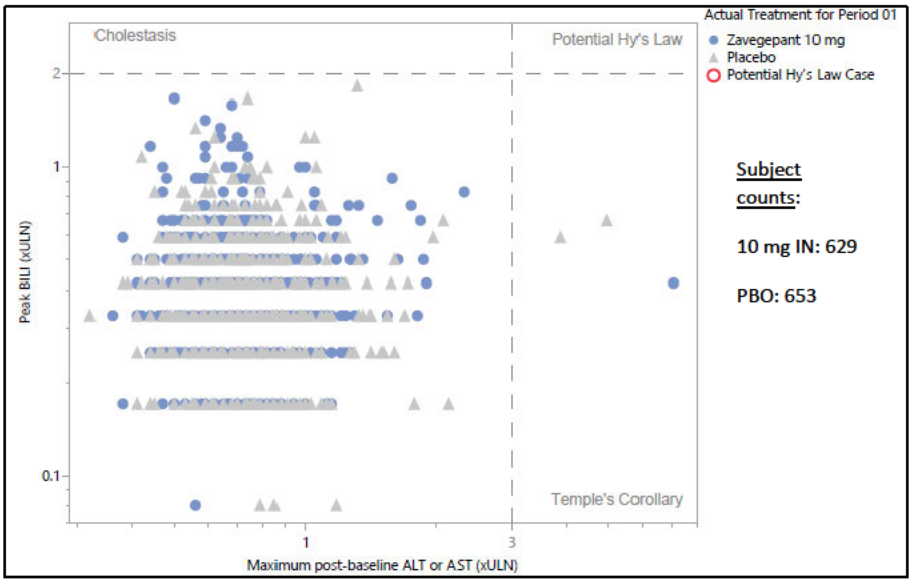


Figure 5: eDISH scatterplot (peak TB x ULN vs. peak ALT or AST x ULN) for study BHV3500-301[19]

4.2.1.3 **BHV3500-202**: This open label, long term safety trial had 19 subjects fall outside the left lower quadrant but none in the Hy's Law quadrant. (**Figure 6**) The one subject with TB > 2 x ULN (ID 047-0821) did not migrate to the right upper quadrant on peak TB versus peak AP scatterplot; thus, elevation in bilirubin was without significant transaminase or AP elevation. The TB was predominantly indirect bilirubin suggesting Gilbert's. The other 18 subjects in Temple's Corollary were adjudicated for DILI and described in Section 4.3.

[18] Produced by DILI Team (Doug Warfield) using JMPClinical and BHV3500-201 adlb dataset
[19] Produced by DILI Team (Doug Warfield) using JMPClinical and BHV3500-301 adlb dataset

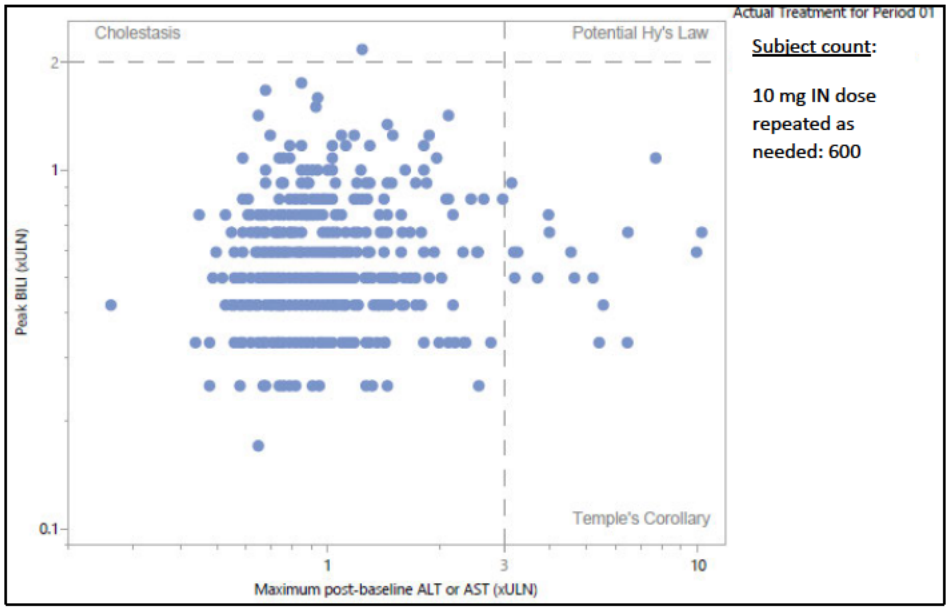
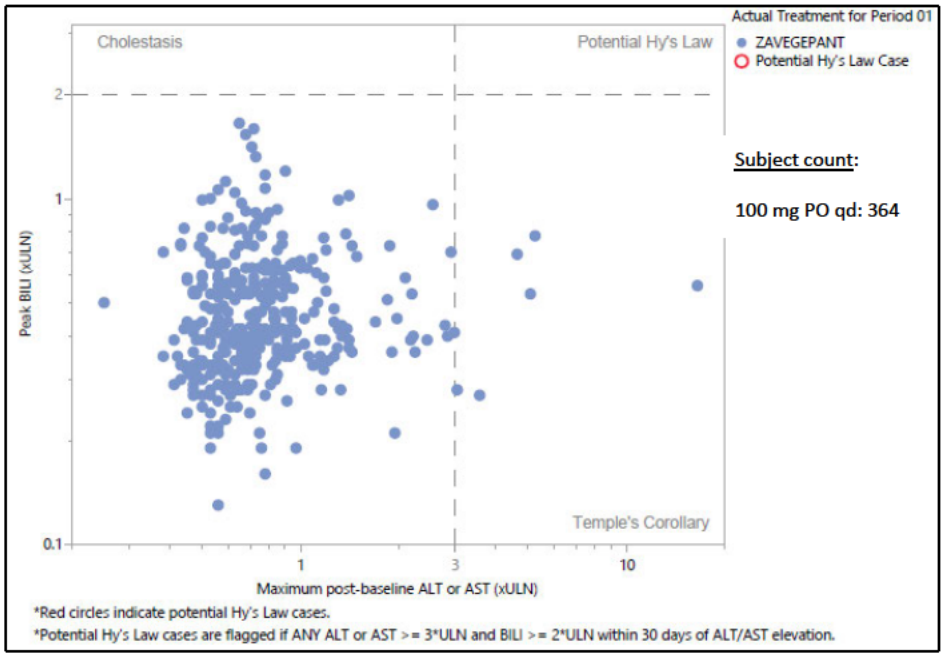


Figure 6: eDISH scatterplot (peak TB x ULN vs. peak ALT or AST x ULN) for study BHV3500-202[20]

4.2.1.4 **BHV3500-106**: This phase 1 open-label, single arm, study of oral ZGNT in healthy volunteers had five subjects falling outside the left lower quadrant and no subjects with TB > 2x ULN in the eDISH scatter plot for hepatocellular injury. (**Figure 7**) These subjects were adjudicated for DILI and described in section 4.3. No subjects fell outside the left lower quadrant on peak TB versus peak AP scatter plot (not shown).

Figure 7: eDISH scatterplot (peak TB x ULN vs. peak ALT or AST x ULN) for study BHV3500-106[21]



[20] Produced by DILI Team (Doug Warfield) using JMPClinical and BHV3500-202 adlb dataset
[21] Produced by DILI Team (Doug Warfield) using JMPClinical and BHV3500-106 adlb dataset

4.3 Case level analysis: The DILI Team assessed 32 cases of potential DILI across the four studies. Besides the enzyme criteria reflected in the scatter plots (i.e., peak AP >2x ULN, peak ALT or AST >3 ULN and peak TB> 2 x ULN), subjects identified with liver related severe adverse events were included in this group of 32. Of the 32, we deemed 27 as unlikely DILI or indeterminate. Alternate diagnoses were myopathy (12), unknown (8), COVID-19 (2), other viral infections (2), Gilbert's (1), amoxicillin-clavulanate liver injury (1) and spurious lab result (1).

Of the remaining five, only one was consider probable DILI due to ZGNT (see Section 4.3.1). The other four were considered possible. (**Table 5**) Overall, the liver injuries were mild with a median peak ALT of 153 U/L with a maximum of 310 U/L. There was no hyperbilirubinemia and thus no Hy's Law cases.

Table 5: Clinical characteristics of subjects with at least possible DILI due to ZGNT[22]

#	ID	Study	Causality Score*	Alternate diagnosis	Age (yr)	Sex	Race	Hy's Law	Latency from start drug (da)	Latency from stop drug (da)	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)^	Bilirubin peak (mg/dL)	R value peak (ALT)**	Washout ALT normal (da)	Washout AST normal (da)
1	(b) (6)	BHV3500-301	3	NA	25	M	Black AA	No	7	6	310	120	104	0.3	9.12	NA	13
2		BHV3500-106	4	Viral URI	27	F	White	No	49	[7]	100	76	104	0.3	2.94	28	28
5		BHV3500-202	4	AIH	28	F	White	No	136	6	153	90	104	0.6	4.50	NA	96
3		BHV3500-202	4	Unknown	44	F	White	No	223	12	183	105	104	0.5	5.38	79	56
4		BHV3500-202	4	Unknown	33	M	Hispanic	No	225	[99]	138	73	104	0.6	4.06	35	35
				Mean	*31.4*				*128.0*	*[16.4]*	*177*	*93*	*104*	*0.5*	*5.2*	*47.3*	*45.6*
				Std dev	*6.83*				*88.7*	*41.8*	*72*	*18*	*0*	*0.1*	*2.1*	*22.6*	*28.8*
				Median	*28*				*136.0*	*6*	*153*	*90*	*104*	*0.5*	*4.5*	*35*	*35*
				Min	*25*				*7*	*[99]*	*100*	*73*	*104*	*0.3*	*2.9*	*28*	*13*
				Max	*44*				*225*	*12*	*310*	*120*	*104*	*0.6*	*9.1*	*79*	*96*

NA = not available or not applicable
Viral URI = viral upper respiratory infection
AIH = autoimmune hepatitis
R-value = (ALT/ULN) ÷ (AP/ULN); R > 5: hepatocellular; R between 2 & 5 mixed; R < 2 cholestatic
*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate
^For purposes of R-value calculations, the ULN (104) was imputed if AP never rose to > ULN
** ULNs used for R-values: ALT 34 U/L, AST 34 U/L, AP 104 U/L, TB 1.2 mg/dL
~[ ] day values means the drug continued for that many days *after* injury onset.

4.3.1 Subject (b) (6) (probable DILI): We discuss this case in detail because it was the only case we assessed as probable liver injury from ZGNT.

Case summary: This subject was a 25-year-old African-American man who had elevation in aminotransaminases without hyperbilirubinemia seven days after taking intranasal (IN) ZGNT (10 mg).

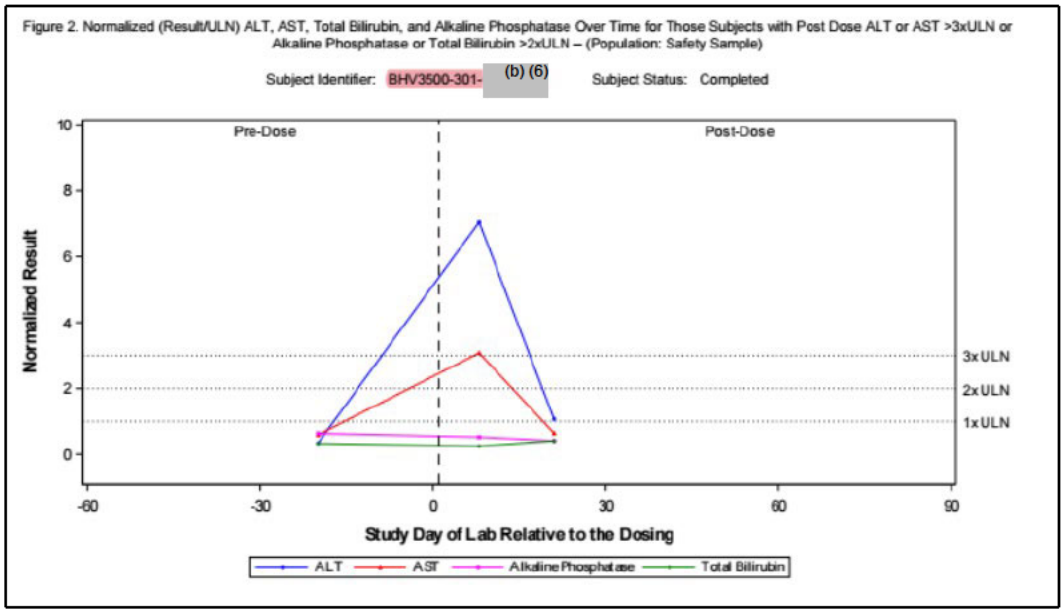
At baseline, he had a BMI of 22.5 kg/m^2. He did not drink alcohol. His ALT, AST, AP, and TB were 15 U/L, 23 U/L, 82 U/L and 0.4 mg/dL, respectively. He took no other medications. There was no mention of herbal or dietary supplement (HDS) use.

[22] Table made by DILI Team

He enrolled in Study BHV3500-301 on [redacted] (b) (6) (Day 0) and took his first and only dose of IN ZGNT on [redacted] (b) (6) (Day 14). He received no further doses per protocol. On [redacted] (b) (6) (Day 21), at the end-of-study visit, his ALT was 310 U/L, AST 120 U/L, AP 68 U/L and TB 0.3 mg/dL. CK and LDH were 165 U/L and 221 U/L respectively. He was asymptomatic. Thereafter, liver enzymes fell to nearly normal (1.1 x ULN) for ALT and normal for AST within 13 days ([redacted] (b) (6) Day 34). TB and AP remained normal throughout the study. (**Figure 8**)

Serologies were negative for hepatitis A, B, C, and E. Acute CMV and EBV serologies were also negative. ANA and ASMA were negative. No imaging was done.

Figure 8: Line gaph of liver biochemistries over time for subject [redacted] (b) (6) [23]



Case Assessment: This is probable DILI due to ZGT. Evaluation testing was adequate except no imaging. Transient quick passage of a stone may compete, but he was asymptomatic, and he does not carry obvious risk factors for stone disease. He is a young man with a BMI of 22.5 kg/m^2. Enzyme elevation was mild and transient without repeat dosing of IN ZGNT.

5.0 Assessment and Recommendations:

5.1 Assessment: Zavegepant (ZGNT) is a small molecule, calcitonin gene-related peptide receptor antagonist (CGRP-ra) delivered as needed intranasally (IN) for the treatment of migraine headaches. Two CGRP-ra's in development had significant hepatotoxicity issues and were abandoned for further development several years ago. Since then, three CGRP-ra's have successfully been marketed for acute treatment or prevention of migraines. The three approved agents (atogepant, rimegepant, ubrogepant) are delivered either orally or sublingually. ZGNT would be the first CGRP-ra delivered IN, thus bypassing the portal circulation on initial pass. None of the three

[23] NDA216386 (216386 - 0021 - (21) - 2022-11-15 - ORIG-1 /Clinical/Response To Information Request) - External Liver Panel Committee Correspondence - Initial (#340)

marketed agents are labeled for hepatotoxicity risk. The DILI Team consulted on atogepant pre-marketing[24] and rimegepant post-marketing.[25] The DILI team concluded that these agents posed a low risk for severe hepatotoxicity.

Non-clinical data for ZGNT do not suggest a significant risk of DILI, but not all in vitro studies related to DILI risk were found in this application. There was no time-dependent inhibition of CYP3A4, ZGNT's primary metabolizing CYP. Only a few metabolites were identified, but we found no glutathione trapping studies to inform us on metabolite reactivity. ZGNT does not bind BSEP or MRP2 transporters. We found no mitochondrial inhibition data. While some increase in liver biochemistries were seen in animal studies, these elevations did not correlate with significant histopathology.

Clinical data also do not suggest IN ZGNT has a significant DILI risk. There were no differences in liver enzyme elevations between treatment and placebo arms in the two randomized, controlled studies. However, these data were limited to trials in which a single dose of IN ZGNT was administered. There were modest aminotransferase elevations noted in the single arm, open label safety study that permitted subjects to take repeat IN ZGNT daily doses up to eight days per month. Healthy volunteers taking oral ZGNT for eight weeks also had modest elevations in aminotransferases. Across all four studies, only five subjects had possible or probable DILI due to ZGNT following detailed case analyses. All elevations in aminotransferases possibly due to ZGNT were modest without hyperbilirubinemia. There were no Hy's Law cases or cases of significant cholestatic liver injury.

Thus, ZGNT can cause aminotransferase elevations, but we suspect the *pre re nata* (PRN) use of 10 mg IN ZGNT, limited to eight days per month, lessens the risk for liver injury by limiting exposure. If there is a propensity for patients to use IN ZGNT substantially more often than prescribed, it is conceivable that significant liver injury could arise post-market. However, the single arm safety study of healthy volunteers receiving 100 mg daily by mouth for eight weeks offers some reassurance of low DILI risk. According to the sponsor, 100 mg daily by mouth carried similar exposure as 10 mg daily given intranasally by C_{max} and AUC $_{0\text{-}24}$.[26]

Overall, the non-clinical and clinical trial data both suggest a low concern for significant DILI with PRN intranasal ZGNT. We do not recommend substantial labeling for hepatotoxicity or post-market research beyond routine pharmacovigilance.

5.2 Recommendations

1. DILI risk should not hold up approval of this NDA

[24] Open DARRTS session first to enable following link to work: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8061050a
[25] Open DARRTS session first to enable following link to work: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806ae16a
[26] NDA216386 (216386 - 0001 - (1) - 2022-03-09 - ORIG-1 /Multiple Categories/Subcategories) - 16.1.1 Protocol and Amendments (#14)

2. Unless there is a concern for substantially more frequent use of IN ZGT post-market compared to dosing used in the pivotal trials, we do not recommend PMR beyond routine pharmacovigilance, labeling for hepatotoxicity, or routine monitoring of liver biochemistries.

Paul H. Hayashi -S

Digitally signed by Paul H. Hayashi -S
Date: 2023.02.09 15:36:14 -05'00'

(Signing for Dr. Ling in her absence and with her agreement.)

Ling Lan, MD, PhD
Clinical Analyst, DILI Team, Division of Hepatology and Nutrition
CDER/OND

Paul H. Hayashi -S

Digitally signed by Paul H. Hayashi -S
Date: 2023.02.09 15:36:41 -05'00'

Paul H. Hayashi, MD, MPH
DILI Team Lead, Division of Hepatology and Nutrition
CDER/OND

Frank A. Anania -S

Digitally signed by Frank A. Anania -S
Date: 2023.02.09 15:55:24 -05'00'

Frank Anania, MD
Acting Director, Division of Hepatology and Nutrition
CDER/OND

Appendix: Trial Schematics

Figure A: Study BHV3500-301, Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy Trial of BHV-3500 (zavegepant) intranasal (IN) for the Acute Treatment of Migraine. Single dose study.[27]

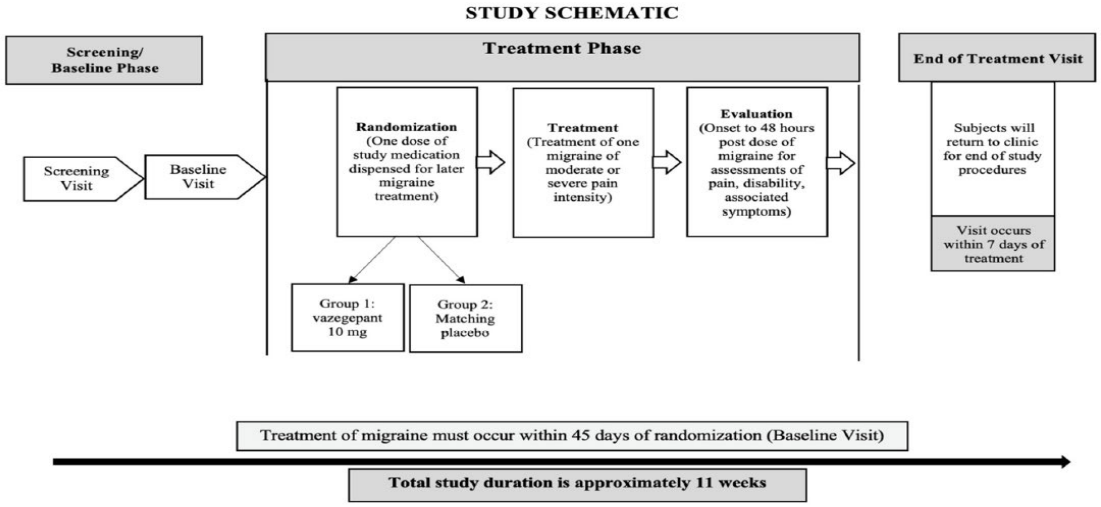
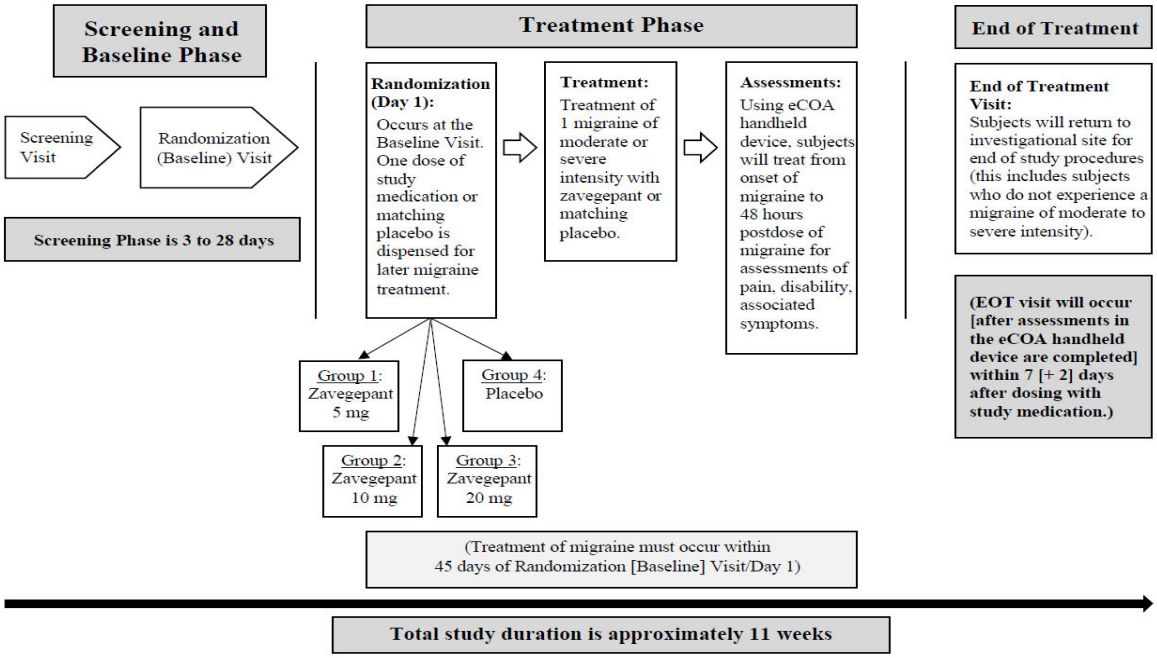


Figure B: Study BHV3500-201, Phase 2/3, Double-blind, randomized, placebo-controlled, dose-raning study to evaluate the efficacy and safety of zavegepant (IN) for the acute treatment of a single moderate to severe migraine. Single dose study.[28]



[27] NDA216386 (216386 - 0011 - (11) - 2022-08-19 - ORIG-1 /Quality/Response To Information Request) - 16.1.1 Protocol and Amendments (#245)
[28] NDA216386 (216386 - 0011 - (11) - 2022-08-19 - ORIG-1 /Quality/Response To Information Request) - 16.1.1 Protocol and Amendments (#216)

Figure C: Study BHV3500-202, A Phase 2/3 Open-label, Long-Term, Safety Trial of BHV3500 (zavegepant) Intranasal (IN) for the Acute Treatment of Migraine.[29]

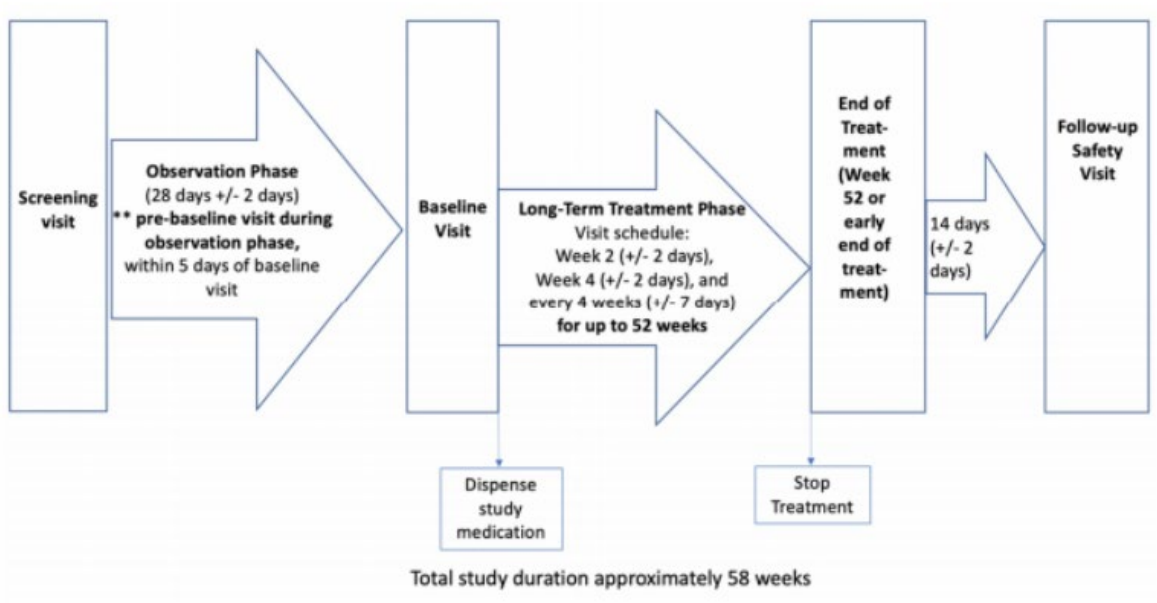
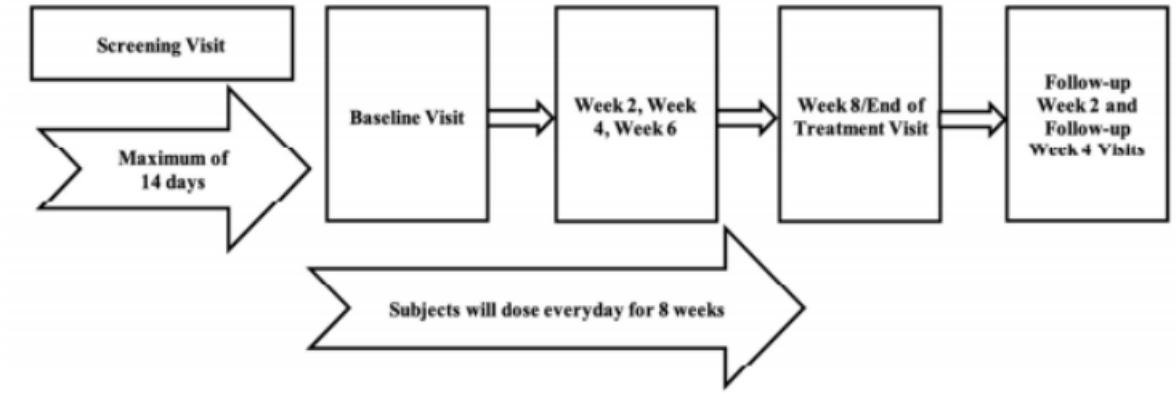


Figure D: BHV3500-106, Phase 1 Open-label, 8-week Safety Study of Oral Zavegepant (BHV-3500) in Normal Healthy Subjects[30]



[29] NDA216386 (216386 - 0011 - (11) - 2022-08-19 - ORIG-1 /Quality/Response To Information Request) - 16.1.1 Protocol and Amendments (#81)
[30] NDA216386 (216386 - 0001 - (1) - 2022-03-09 - ORIG-1 /Multiple Categories/Subcategories) - 16.1.1 Protocol and Amendments (#248)

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/

PAUL H HAYASHI
02/09/2023 04:45:19 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

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 8, 2023
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 216386
Product Name and Strength:	Zavzpret (zavegepant) nasal spray, 10 mg
Applicant/Sponsor Name:	Pfizer Inc.
TTT ID #:	2022-2755
OSE RCM #:	2022-501-2
DMEPA 2 Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

Biohaven submitted revised professional sample and trade blister labeling and carton labeling received on November 8, 2022 (DARRTS record date November 7, 2022) for Zavzpret (zavegepant) nasal spray to revise the package term from (b) (4) to "unit dose" and the salt equivalency statement from (b) (4) to "10.6 mg of zavegepant HCl." These revisions are in response to an information request sent by the Agency on October 27, 2022.[a]

Then on December 5, 2022, the Biohaven notified the Agency that sponsorship, all rights, and holder responsibilities for NDA 216386 were transferred from Biohaven Pharmaceutical Holding Company Ltd to Pfizer. Accordingly, Pfizer submitted revised professional sample and trade blister labeling and carton labeling received on December 7, 2023, to reflect this change in Sponsorship as well as to propose minor editorial revisions to the professional and trade devise container labels.

Lastly, Pfizer submitted revised carton labeling received on February 1, 2023, to revise the inactive ingredient from (b) (4) to "dextrose" to be in accordance with "USP

[a] https://panorama.fda.gov/document/view?ID=635af25e00e788817a4854caaaec9b02

<1091> Labeling of inactive ingredients. This revision is in response to an information request sent by the Agency on January 26, 2023.[b]

The Division of Neurology 2 (DN 2) requested that we review the revised professional sample and trade labels and labeling for Zavzpret (Appendix A) to determine if they are acceptable from a medication error perspective.

2 ASSESSMENT AND CONCLUSION

The Applicant implemented all recommendations from the October 27, 2022, and January 26, 2023, information requests. In addition to the Agency's requested recommendations, the Applicant updated the labels and labeling to reflect the change in Sponsorship from Biohaven Pharmaceutical Holding Company Ltd to Pfizer as well as minor editorial revisions to the professional and trade device container labels.

Our review of the revised professional sample and trade blister labeling, carton labeling and device container labels determined they are acceptable from a medication error perspective, and we have no additional recommendations at this time.

[b] https://panorama.fda.gov/document/view?ID=63d2a8a700b4cf223b953f9288ec8f2f

APPENDIX A. LABEL AND LABELING

A.1 List of Labels Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Zavzpret labels and labeling submitted by Pfizer.

- Commercial Presentation
  - Container label (device label) received on December 7, 2023
  - Blister labeling (foil backing) received on December 7, 2023
  - Carton labeling (6 count) received on February 2, 2023

- Professional Sample Presentation
  - Container label (device label) received on December 7, 2023
  - Blister labeling (foil backing) received on December 7, 2023
  - Carton labeling (1 count) received on February 2, 2023

A.2 Label and Labeling Images

(b) (4)

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

---

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/

BEVERLY WEITZMAN
02/08/2023 03:17:04 PM

STEPHANIE L DEGRAW
02/08/2023 08:53:04 PM

Clinical Inspection Summary

Date	1/3/2023
From	Cara Alfaro, Pharm.D., Clinical Analyst Phillip Kronstein, M.D., Team Leader Jenn Sellers, M.D., Ph.D. (Acting) Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Lana Chen, R.Ph., Regulatory Project Manager Ryan Kau, M.D., Medical Officer Heather Fitter, M.D., Team Leader Division of Neurology 2 Office of Neuroscience
NDA #	216386
Applicant	Biohaven Pharmaceuticals, Inc.
Drug	Zavegepant
NME	Yes
Proposed Indication	Acute treatment of migraine with or without aura in adults
Consultation Request Date	6/9/2022
Summary Goal Date	1/9/2023
Priority/Standard Review	Standard
Action Goal Date	3/9/2023
PDUFA Date	3/9/2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. DeFeria, Mendes, Raad, and Rubino as well as the contract research organization (CRO), (b) (4) were inspected in support of this NDA and covering Protocols BHV3500-201 and BHV3500-301. The studies appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

Zavegepant nasal spray is being developed under NDA 216386 (IND 134120) for the acute treatment of migraine with or without aura in adults. The sponsor has submitted the results of a Phase 2 study (BHV3500-201) and a Phase 3 study (BHV3500-301) to support the efficacy and safety of zavegepant for this indication.

Protocol BHV3500-201

Title: "Phase II: double-blind, randomized, placebo controlled, dose-ranging trial of BHV-3500 for the acute treatment of migraine"

Subjects: 1588

Sites: 82 sites in the United States

Study Initiation and Completion Dates: 3/25/2019 to 11/11/2019

This was a double-blind, randomized study in subjects with moderate or severe migraine. Main eligibility criteria included male or females ≥18 years of age; minimum of 1 year history of migraines (with or without aura) consistent with an International Classification of Headache Disorders, 3rd Edition; age of onset of migraine attacks <50 years of age; migraine attacks, on average, lasting 4 to 72 hours if untreated; not >8 attacks of moderate or severe intensity per month within last 3 months; at least 2 consistent migraine headache attacks of moderate or severe intensity in each of the 3 months prior to the screening visit and throughout the screening period; <15 days with headaches (migraine or non-migraine) per month in each of the 3 months prior to the screening visit and throughout the screening period; and subjects on prophylactic migraine medication are permitted if dose has been stable for at least 3 months prior to the screening visit and unchanged during study.

This study was comprised of 3 phases: screening, double-blind treatment, and end of treatment visit.

Screening Phase (3 to 28 days)
Informed consent and screening procedures to determine of subject eligibility. Subjects were given paper diaries to record concomitant and rescue medication use.

Double-blind Treatment Phase (45 days)
Investigational product (IP) was an Aptar Unidose System (UDS) liquid spray device containing a single dose of zavegepant or placebo.
Subjects were randomized (1:1:1:1), stratified by use of prophylactic migraine medications (yes/no), to one of the following arms:

- Zavegepant 5 mg
- Zavegepant 10 mg
- Zavegepant 20 mg
- Placebo

Subjects were instructed on the proper use of the Aptar UDS device. Subjects were instructed to use one spray into one nostril after experiencing a moderate or severe migraine headache.

Subjects were provided with the electronic diary (eDiary) and instructed on its use. The eDiary was used to record answers about the subject's migraine symptoms upon experiencing a moderate or severe migraine headache. Subjects were to complete assessments on the eDiary for 48 hours after taking IP.

After dosing with IP, all other headache medication was prohibited for the first 2 hours. Subjects who did not experience relief of their migraine headache at the end of the 2 hours were permitted to rescue medications listed in the protocol. Subjects recorded concomitant and rescue medication use in paper diaries provided by the site.

End of Treatment Visit
Subjects returned to the clinical site for end of study procedures within 7 days after dosing with IP.

The co-primary efficacy endpoints were pain freedom and freedom from most bothersome symptom (MBS) at two hours post dose.

Protocol BHV3500-301

Title: "Phase 3: double-blind, randomized, placebo controlled, safety and efficacy trial of BHV-3500 (zavegepant) intranasal (IN) for the acute treatment of migraine"

Subjects: 1282

Sites: 87 sites in the United States

Study Initiation and Completion Dates: 10/27/2020 to 10/22/2021

This was a double-blind, randomized study in subjects with moderate or severe migraine. Main eligibility criteria were the same as for Protocol BHV3500-201.

This study was comprised of 3 phases: screening, double-blind treatment, and end of treatment visit. These phases were the same as that for Protocol BHV3500-201, with the exception that subjects were randomized to one of two study arms:

- Zavegepant 10 mg
- Placebo

The co-primary efficacy endpoints were pain freedom and freedom from most bothersome symptom (MBS) at two hours post dose.

Rationale for Site Selection

Sites were chosen for BIMO inspections based on risk ranking in the Clinical Investigator Site Selection Tool (CISST), numbers of enrolled subjects in the dose of interest, and prior inspection history.

III. RESULTS

1. **Armando DeFeria, M.D.**
   Site #94
   Ideal Clinical Research, Inc.
   600 N Hiatus Rd, Suite 203
   Pembroke Pines, FL 33026-5207
   Inspection Dates: 10/3/2022 – 10/7/2022

   At this site for Protocol BHV3500-301, 39 subjects were screened, 29 subjects were randomized, and 28 subjects completed the study. One subject discontinued the study due to withdrawal of consent.

   Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and co-primary efficacy data (pain freedom, freedom from most bothersome symptom [MBS]).

   The co-primary efficacy endpoints were pain freedom and freedom from MBS at two hours post investigational product (IP) dose. Subjects entered efficacy data into an eDiary provided by the vendor, ERT. Source data was available at the site in the form of paper printed from the web-based database portal and a USB drive provided by the sponsor to the site. Efficacy data was reviewed for all 29 randomized subjects; no discrepancies were identified. There was no evidence of underreporting of adverse events.

2. **Antonio Mendes, M.D.**
   Boston Clinical Trials, LLC
   26 Cummins Highway
   Boston, MA 2131
   Inspection Dates: 10/31/2022 – 11/3/2022

   At this site for Protocol BHV3500-301, 67 subjects were screened, 59 subjects were randomized, and 58 subjects completed the study. One subject discontinued the study due to loss to follow-up.

   Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for 20 of 59 (34%) randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results,

concomitant medications, and protocol deviations.

Efficacy data was reviewed for all 59 randomized subjects. The co-primary efficacy endpoints were pain freedom and freedom from MBS at two hours post IP dose. Subjects entered efficacy data into an eDiary provided by the vendor, ERT. Source data was available at the site in the form of paper printed from the web-based database portal and a USB drive provided by the sponsor to the site. No discrepancies were identified. There was no evidence of under-reporting of adverse events.

3. George Raad, M.D
Accellacare
1700 Abbey Place, Suite 201
Charlotte, NC 28209-3734
Inspection Dates: 10/3/2022 – 10/5/2022

At this site for Protocol BHV3500-201, 47 subjects were screened, 34 subjects were randomized, and 34 subjects completed the study.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and co-primary efficacy data (pain freedom, freedom from most bothersome symptom [MBS]).

The co-primary efficacy endpoints were pain freedom and freedom from MBS at two hours post IP dose. Subjects entered efficacy data into an eDiary provided by the vendor, ERT. Source data was available at the site in the form of paper printed from the web-based database portal and a CD provided by the sponsor to the site. Efficacy data was reviewed for all 34 randomized subjects; no discrepancies were identified. There was no evidence of under-reporting of adverse events.

4. John Rubino, M.D
Accellacare of Raleigh, LLC
3521 Haworth Drive, Suite 100
Raleigh, NC 27609
Inspection Dates: 10/11/2022 – 10/14/2022

At this site for Protocol BHV3500-201, 49 subjects were screened, 41 subjects were randomized, and 41 subjects completed the study.

Signed informed consent forms, dated prior to participation in the study, were present for all

subjects who were screened. An audit of the study records for all subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and co-primary efficacy data (pain freedom, freedom from most bothersome symptom [MBS]).

The co-primary efficacy endpoints were pain freedom and freedom from MBS at two hours post IP dose. Subjects entered efficacy data into an eDiary provided by the vendor, ERT. Source data was available at the site in the form of paper printed from the web-based database portal and a CD provided by the sponsor to the site. Efficacy data was reviewed for all 41 randomized subjects No discrepancies were identified. There was no evidence of under-reporting of adverse events.

5. (b) (4)

Inspection Dates: 11/14/2022 – 11/17/2022

The inspection covered responsibilities transferred to the contract research organization (CRO) (b) (4) from the sponsor, Biohaven Pharmaceuticals, Inc. The inspection covered site monitoring, project management, and data management related to Protocol BHV3500-301 and focused on the two clinical investigator sites chosen for inspection for this protocol. Of note, the CRO (b) (4) and not (b) (4) performed site monitoring for Protocol BHV3500-201.

Study records reviewed included, but were not limited to, transfer of regulatory obligation (TORO); trial master file (TMF); SOPs; organization and personnel; selection of monitors; monitoring procedures and reports; electronic data capture (EDC) system development; record retention; project management; data management, and data transfer agreements.

A total of 90 clinical sites enrolled subjects in Protocol BHV3500-301. (b) (4) was responsible for site monitoring for this protocol. Monitoring visits were conducted according to the monitoring plan and SOPs. According to (b) (4) no clinical sites were terminated during the conduct of the study for noncompliance or other issues. Site monitoring also included assessment of eDiary compliance and review of subject eDiary entries. The vendor, ERT, was responsible for technical support for the eDiaries and data from the eDiaries went from ERT directly to the sponsor.

The data management plan outlined how (b) (4) collected, coded, reviewed, and locked the data for Protocol BHV3500-301. The data management plan included monthly data transfers from (b) (4) through a secured website, to the statistics vendor (b) (4) No issues regarding data management were identified during the inspection.

{See appended electronic signature page}

Cara Alfaro, Pharm.D.
Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
(Acting) Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Document Room/NDA #216386
Division of Neurology 2/Division Director/Nick Kozauer
Division of Neurology 2/Deputy Division Director/Paul Lee
Division of Neurology 2/Medical Team Leader/Heather Fitter
Division of Neurology 2/Medical Officer/Ryan Kau
Division of Neurology 2/Project Manager/Lana Chen
OSI/Office Director/David Burrow
OSI/Office Deputy Director/Laurie Muldowney

OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/GCPAB/Acting Branch Chief/Jenn Sellers
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Clinical Analyst/Cara Alfaro
OSI/DCCE/GCPAB Program Analyst/Yolanda Patague
OSI/DCCE/GCPAB Program Analyst/Loreto-Corazon Lim

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/

CARA L ALFARO
01/03/2023 11:50:40 AM

PHILLIP D KRONSTEIN
01/03/2023 03:28:39 PM

JENN W SELLERS
01/03/2023 03:39:32 PM

M E M O R A N D U M

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

Date: December 21, 2022

To: Nick Kozauer, M.D., Director
Division of Neurology II
Office of Neuroscience

Through: Joshua Lloyd, M.D., Medical Officer Team Leader
Controlled Substance Staff

Dominic Chiapperino, Ph.D., Director
Controlled Substance Staff

From: Steven Galati, M.D., Medical Officer
Controlled Substance Staff

Subject: **Drug:** BHV-3500 (Zavegepant)
NDA: 216386
Indication: Treatment of acute migraine in adults
Dosage: Intranasal (IN) 10 mg solution, single spray
Sponsor: Biohaven Pharmaceuticals, Inc.
PDUFA Goal Date: March 9, 2023

Materials Reviewed:

- Original NDA submission, submitted March 9, 2022, and relevant subsequent amendments
- CSS Review Document for IND 134120 dated April 28, 2020, completed by Jovita Randall-Thompson, Ph.D.
- CSS Review Document for IND 134120 dated July 23, 2020, completed by James Tolliver, Ph.D.
- PubMed Search for calcitonin gene-related peptide (CGRP) receptor antagonists

Table of Contents

I. EXECUTIVE SUMMARY

1. Background

This memorandum responds to a consult request from the Division of Neurology II (DN2) for the Controlled Substance Staff (CSS) to review the New Drug Application (NDA) for BHV-3500 (Zavegepant), as well as the proposed labeling. BHV-3500 is an intranasal (IN) formulation that was developed under IND 134120 with a proposed indication as a treatment for migraines in adults using a commercially available single-dose spray device (b) (4) (b) (4) that delivers (b) (4) µL dosing volume. Throughout this review, the drug product will be referred to as BHV-3500.

Migraine is a common and debilitating neurological disorder that affects approximately 15% of the adult population. It is characterized by moderate-to-severe episodic unilateral pulsating headaches, which may be associated with nausea and/or photophobia and phonophobia. Currently, there are two approved orally administered calcitonin gene-related peptide (CGRP) receptor antagonists used to treat migraines in adults, Rimegepant (Nurtec, NDA 212728) and Ubrogepant (Ubrelvy, NDA 211765), which are not scheduled under the Controlled Substances Act (CSA). The Applicant believes the IN route, utilized in their formulation, is an advantage over existing oral formulations given approximately half of migraine patients suffer from nausea or vomiting during a migraine.

The proposed product, BHV-3500, is a third-generation, selective, high-affinity, CGRP receptor antagonist developed for the treatment of migraine. CGRP is an endogenous 37 amino acid peptide contained within pain signaling nociceptive afferents that are believed to have a causal role in migraine. Treatment with a CGRP receptor antagonist is thought to relieve migraine by 1) blocking CGRP-induced neurogenic vasodilation (returning dilated intracranial arteries to normal); 2) halting the cascade of CGRP-induced neurogenic inflammation that leads to peripheral sensitization; and/or 3) inhibiting the central relay of pain signals from the trigeminal nerve to the caudal trigeminal nucleus.

An End-of-Phase 2 meeting took place where CSS attended and provided consultation. The original submission package (submitted January 28, 2020 under IND 134120) was missing the submission of abuse-related data. CSS requested a summary of all the abuse-related data,

including animal toxicology and behavioral observations, final study reports of functional activity at abuse-related receptors, and abuse-related adverse events from clinical studies. The Applicant provided the documents as requested. James M. Tolliver, Ph.D. (CSS consultation review dated July 23, 2020) reviewed the submitted documents and concluded there was no abuse potential signal associated with BHV-3500 based on the completed preclinical and clinical studies. The Applicant was informed there was no need to conduct preclinical drug discrimination, intravenous self-administration, or physical dependence studies or human abuse potential studies. The Applicant was also instructed they should still monitor for adverse events indicative of abuse potential, as well as for actual incidences of abuse, misuse, or diversion. CSS further commented that any possible abuse potential observed during the clinical development program may require reconsideration of additional studies required to complete a full abuse potential assessment.

2. Conclusions

- BHV-3500 (Zavegepant) is a high potency calcitonin gene-related receptor peptide (CGRP) antagonist developed by the Applicant for the acute treatment of migraine in a single dose nasal spray formulation.
- Receptor binding studies, previously reviewed by CSS, demonstrated little binding for BHV-3500 to various receptors, channels, and transporters that are relevant to abuse potential.
- No abuse potential studies were conducted or required in support of this application. Review of the abuse-related safety data contained in this application did not demonstrate an abuse potential signal for BHV-3500 and was consistent with the known profile of approved CGRP antagonists (Rimegepant and Ubrogepant), which are not scheduled under the Controlled Substances Act (CSA).
- The review of adverse event data from the clinical trials and the previously reviewed nonclinical studies do not demonstrate a signal of abuse potential associated with BHV-3500, and a scheduling recommendation under the CSA is not required for BHV-3500 at this time.

3. Recommendations

Based on our findings, as captured in the Conclusions section, we recommend the following:

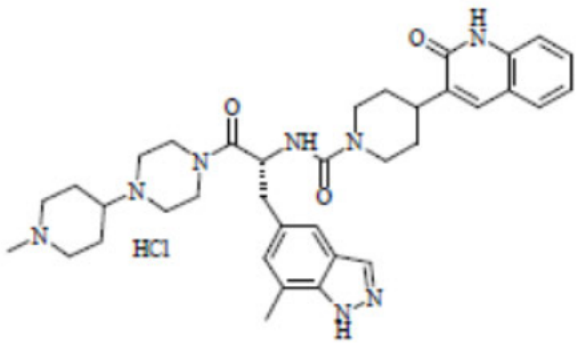
> The preclinical and clinical program for BHV-3500 (Zavegepant) did not reveal any signal for abuse potential, and, therefore, we do not recommend this substance be scheduled under the Controlled Substances Act (CSA). It is further recommended that prescribing information for BHV-3500 omit section 9 Drug Abuse and Dependence from PLR format product labeling.

II. DISCUSSION

1. Chemistry

Substance Information

Name: BHV-3500 (Zavegepant)
Chemical name: (R)-N-(3-(7-methyl-1H-indazol-5-yl)-1-(4-(1-methylpiperidin-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidine-1-carboxamide hydrochloride
Chemical formula: C36H46N8O3.HCl (HCl salt); C36H46N8O3 (free base)
Molecular weight: 675.26 grams (HCl Salt); 638.82 grams (free base)
Molecular Structure:



Drug Product:
The proposed BHV-3500 product is an IN, 10 mg solution (nasal spray) to be supplied as a disposable single-use unit drug-device combination. The spray is formulated at a concentration of (b) (4) mg/mL for use with a nasal spray device (b) (4) (b) (4) A 10 mg of BHV-500 is delivered on actuation in a volume of (b) (4) ul.

Table 1: Composition of BHV-3500 (Zavegepant) Nasal Spray, 10 mg

Component	Quality Standard	Function	Quantity per (b) (4) dose	
			%	mg
Zavegepant Hydrochloride	In-house Specification[3]	Active	(b) (4)	10.00 mg[3]
Succinic Acid	NF	(b) (4)		
Dextrose (b) (4)	USP			
Hydrochloric Acid[4]	NF/Ph.Eur.			
Sodium Hydroxide[4]	NF/Ph.Eur.			
Water For Injection	USP/Ph.Eur.			
(b) (4) device	Not applicable	Drug Delivery	1 Unit	
(b) (4)				

USP = United States Pharmacopeia
Ph.Eur. = European Pharmacopoeia
NF = National Formulary

Source: Applicant's Description and Composition of the Drug Product document, p.1

2. Nonclinical Pharmacology

Previously submitted nonclinical data were reviewed by Jovita Randall-Thompson, Ph.D. under IND 134120 dated April 28, 2020, and James Tolliver, Ph.D. under IND 134120 dated July 23, 2020. In summary, CSS concluded that the preclinical studies did not reveal an abuse potential signal associated with the drug product. For details, please refer to the respective reviews cited above with note of the details provided in the April 28, 2020 review by Dr. Tolliver.

Established Mechanism of Action

BHV-3500 is a high potency calcitonin gene-related peptide (CGRP) receptor antagonist. The calcitonin gene-related peptide receptor is located in both the central and the peripheral nervous system and has been shown to be involved in neurogenic inflammation and the pathophysiology of migraine.

3. Clinical Pharmacology

Through the IN route, BHV-3500 has a median Tmax of 0.54 hours (range: 0.38 – 0.59 hours) and is primarily eliminated unchanged as the parent compound. Refer to the clinical pharmacology review for a complete discussion of their findings.

4. Clinical Studies

4.1 Scope of Review

The Applicant studied three formulations throughout their clinical program. The IN solution (nasal spray) was developed in early development and was subsequently used in the pivotal clinical studies and for additional clinical pharmacology studies. Oral disintegrating tablets (ODT) and oral soft gelatin capsule formulations were developed and used for additional pharmacokinetic (PK) and safety studies (BHV3500-103 and BHV3500-107); the soft gelatin capsule is also being utilized in an oral migraine prevention study. The IN formulation was used in ten clinical studies (BHV3500-101, BHV3500-102, BHV3500-105, BHV3500-108, BHV3500-109, BHV3500-110, BHV3500-111, BHV3500-201, BHV3500-202, BHV3500-301).

The primary data presented by the Applicant include two single-dose studies in subjects with migraine who were treated with BHV-3500 10 mg IN (Phase 3 study BHV3500-301 and Phase 2/3 study BHV3500-201). In the pivotal, single-dose studies (BHV3500-301 and BHV3500-201), a total of 2,079 unique subjects received a dose of BHV-3500 10 mg IN (1,023 subjects) or placebo (1,056 subjects). Data from these studies are supplemented by the BHV3500-202 long-term safety study (BHV-3500 10 mg IN) in subjects with migraine, and the Phase 1 BHV3500-106 open-label safety study (100 mg oral BHV-3500) in healthy subjects. Data was pooled for review when possible and presented below under section 4.2. Non-pooled studies were also reviewed and summarized under section 4.2.

4.2 Adverse Event Profile Through all Phases of Development

Definition of Potential Abuse-Related Adverse Events (AEs)

- The Applicant defined Preferred-Terms (PTs) used to identify potential drug abuse-related adverse events (AEs) which included > 750 PTs.
    - The list includes the MedDRA Standardized MedDRA Queries (SMQs) for "drug abuse, dependency and withdrawal," considered to have a possibility of being potential drug abuse AEs (over 450 terms). Additionally, the Applicant added additional terms that may identify AEs with the potential for drug abuse (approximately 330 additional terms).
    - The list was extensive and provided in the Applicant's core Statistical Analysis Plan.
    - Dizziness was only included in the potential abuse-related analysis if concomitant euphoria-related AEs were present (**Table 2**).

Table 2: Euphoria-related AE PTs from Clinical Review

PTs
Euphoric mood
Feeling abnormal
Feeling drunk
Feeling of relaxation
Hallucination
Hallucination, auditory
Hallucination, gustatory
Hallucination, olfactory
Hallucination, synaesthetic
Hallucination, tactile
Hallucination, visual
Hallucinations, mixed
Inappropriate affect
Thinking abnormal

Source: Core Statistical Analysis Plan, p.68

Summary of Analysis of Abuse-related Adverse Events Reported in the Applicant's Completed Studies

Approximately 4,123 unique subjects received BHV-3500 or placebo in Phase 1 studies in either healthy subjects or subjects with migraine, and in Phase 2 and 3 studies in subjects with migraine. A total of 1,588 unique subjects have received BHV-3500 10 mg IN in the single-dose pivotal efficacy studies and long-term safety migraine study for the acute treatment of migraine. In the pivotal, single-dose studies (BHV3500-301 and BHV3500-201), a total of 2,079 unique subjects received a single dose of BHV-3500 10 mg IN (1,023 subjects) or placebo (1,056 subjects). The placebo-controlled studies included over 2000 subjects and the reported PTs with a potential for drug abuse were similar for BHV-3500 10 mg (1.5%) as compared to placebo (1.8%).

The potential for treatment with BHV-3500 to result in withdrawal or rebound was not directly studied. However, no AEs for PTs in the MedDRA SMQ for "drug withdrawal" were identified across the clinical development program. There was no evidence of rebound or withdrawal identified during the follow-up periods of the single-dose studies in subjects with migraine (BHV-3500 10 mg IN); long-term safety study (BHV-3500 10 mg IN); or the Phase 1, 8-week daily dosing safety study (BHV-3500 100 mg oral formulation). Regardless, significant withdrawal symptoms would not be expected with the intended clinical use of a single-dose drug product.

Phase 1 Studies:

The Applicant completed 10 Phase 1 studies, which included 746 subjects, including healthy subjects (N = 699), subjects in specific populations (e.g., moderate hepatic impairment; N = 8), and subjects with migraine (N = 39).

Table 3: Completed Phase 1 Studies

Study	Study Objective(s)	Population PK[a]
Phase 1 Clinical Studies: Biopharmaceutics Bioavailability		
Not applicable	---	---
Phase 1 Clinical Studies: Pharmacokinetics in Normal Healthy Subjects		
BHV3500-101	Safety, tolerability, PK, and QT assessment of single-ascending doses IN zavegepant	X
BHV3500-102	Safety, tolerability, MTD, PK, and QT assessment of multiple-ascending doses IN zavegepant	X
BHV3500-104	Safety, tolerability, absolute bioavailability, IV PK, ^{14}C-ADME	X
BHV3500-106	Safety, tolerability, and sparse PK of daily dosing of oral zavegepant for up to 8 weeks	X[b]
BHV3500-107	Safety, tolerability, PK of single and multiple ascending doses of oral zavegepant, and food effed on oral zavegepant PK	X[c]
Phase 1 Clinical Studies: Pharmacokinetics in Subjects with Migraine		
BHV3500-105	Safety, tolerability, and PK of single-dose IN zavegepant during migraine and non-migraine state	X
Phase 1 Clinical Studies: Intrinsic Factor Pharmacokinetics		
BHV3500-108	Effects of hepatic impairment of PK of IN zavegepant	X
Phase 1 Clinical Studies: Extrinsic Factor Pharmacokinetics		
BHV3500-109	Effects of multiple doses of IN zavegepant on single-dose PK of an oral contraceptive, and safety and tolerability of IN zavegepant + an oral contraceptive	X
BHV3500-110	Effects of IN zavegepant and concomitant sumatriptan on resting blood pressure, PK, safety, tolerability	X
BHV3500-111	Effects of multiple-dose administration of a strong CYP3A4 inducer (rifampin) on single-dose PK of oral zavegepant and effects of multiple-dose administration of a strong CYP3A4 inhibitor (itraconazole) on single-dose PK of IN and oral zavegepant	X

[a] "X" identifies the studies that were used to support PPK modeling.
[b] PPK validation dataset only
[c] ODT data not included in PPK modeling.
Abbreviations: ^{14}C-ADME = ^{14}C-labeled absorption, distribution, metabolism; and excretion; CYP3A4 = cytochrome P450 3A4; IN = intranasal; IV = intravenous; MTD = maximum tolerated dose; PK = pharmacokinetics; PPK= population PK

Source: Table-1, Clinical Overview p.17

BHV3500-101 was a Phase 1, single-center, placebo-controlled, randomized, double-blind, sequential, single-ascending dose (SAD) study. Dosing of BHV-3500 ranged from 0.1 mg to 40 mg IN in 72 healthy subjects.

BHV3500-102 was a safety, Phase 1, single-center, placebo-controlled, randomized, double-blind, sequential multiple-ascending dose (MAD) study. BHV-3500 was dosed daily via IN route for 14 days with doses ranging from 10 to 20 mg in 72 subjects. The primary objective of the study was to evaluate the safety and tolerability of BHV-3500 following IN administration of MADs ranging from 5 to 40 mg in healthy subjects.

These pooled Phase 1 studies (BHV3500-101 and BHV3500-102) used the IN formulation and included 110 healthy subjects; 39 subjects who received BHV-3500 at a dose below 10 mg (0.1, 0.3, 1, 3, or 5 mg), 15 subjects who received BHV-3500 10 mg, and 56 subjects who received BHV-3500 at a dose above 10 mg (20 mg; 20 mg [10 mg in each nostril]; or 40 mg [20 mg in each nostril with or without time in between nostrils]). Thirty-four subjects received placebo. AEs associated with potential for drug abuse were reported in seven subjects who received BHV-3500 (6.4%) and in one placebo subject (2.9%). The most common reported potential abuse-related AE was somnolence in three subjects (2.7%). The AEs in the pooled studies appear consistent with the known AE profile of a CGRP receptor antagonist (**Table 4**). Although the available data had a small relative representation of some dosing groups, there was no clear evidence of a dose-response in the frequency of abuse-related AEs.

Table 4: Potential Drug Abuse Adverse Events in Intranasal SAD/MAD Healthy Volunteer Pool - Phase 1 Studies BHV3500-101/102

Intensity Preferred Term: n (%)	Zavegepant below 10 mg N = 39	Zavegepant 10 mg N = 15	Zavegepant above 10 mg N = 56	Overall Zavegepant N = 110	Overall Placebo N = 34
Total					
Any AE	1 (2.6)	3 (20.0)	3 (5.4)	7 (6.4)	1 (2.9)
Disturbance in attention	0	1 (6.7)	0	1 (0.9)	0
Fatigue	1 (2.6)	0	0	1 (0.9)	0
Hypoaesthesia	0	0	1 (1.8)	1 (0.9)	1 (2.9)
Somnolence	0	2 (13.3)	1 (1.8)	3 (2.7)	0
Syncope	0	0	1 (1.8)	1 (0.9)	0

Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0
Adverse events (AEs) are listed in alphabetical order by intensity and preferred term.
Zavegepant below 10 mg (i.e., zavegepant 0.1, 0.3, 1, 3, or 5 mg); Zavegepant above 10 mg (i.e., zavegepant 20, 20 [10 in each nostril], 40 [20 in each nostril with or without time in between nostrils]); Overall Zavegepant (i.e., all zavegepant doses pooled); Overall Placebo (i.e., all placebo pooled).

Source: Integrated Summary of Safety, Appendix 2.6.2.2, p.1

Single-Dose Studies in Subjects with Migraine (BHV3500-301 and BHV3500-201):

BHV3500-301 was a Phase 3, double-blind, randomized, placebo-controlled study comparing BHV-3500 10 mg IN to placebo for the acute treatment of moderate to severe migraine. A total of 629 subjects received a single dose of BHV-3500 10 mg IN.

BHV3500-201 was a Phase 2/3, double-blind, randomized, placebo-controlled, dose-ranging study of BHV-3500 compared to placebo for the acute treatment of moderate to severe migraine. This study compared three doses of BHV-3500 (5, 10, and 20 mg) relative to the placebo control. A total of 394 subjects received a single dose of BHV-3500 10 mg IN; 388 subjects received 5 mg IN dose and 403 subjects received the 20 mg IN dose in BHV3500-201. The only potential drug abuse related adverse events reported in at least 1% of subjects in all doses was somnolence in two subjects (0.5%) within the 5 mg IN group, six subjects (1.5%) in the 10 mg IN group, and two subjects (0.5%) in the 20 mg IN group.

Pooled data at the proposed 10 mg IN dose showed no deaths or adverse events leading to discontinuation. AEs categorized as potentially associated with drug abuse were observed with comparable frequency in the BHV-3500 and placebo groups (1.5% and 1.8%, respectively). No AEs were identified for MedDRA PTs in the SMQs of "Drug abuse, dependence and withdrawal."

Table 5: Potential Drug Abuse Related Adverse Events in Phase 2/3 Studies (BHV3500-301 and BHV3500-201)

	BHV3500-301		BHV3500-201		Overall	
Intensity Preferred Term: n (%)	Zavegepant 10 mg N = 629	Placebo N = 653	Zavegepant 10 mg N = 394	Placebo N = 403	Zavegepant 10 mg N = 1023	Placebo N = 1056
Total						
Any AE	6 (1.0)	12 (1.8)	9 (2.3)	7 (1.7)	15 (1.5)	19 (1.8)
Fatigue	3 (0.5)	5 (0.8)	1 (0.3)	0	4 (0.4)	5 (0.5)
Feeling jittery	0	0	0	1 (0.2)	0	1 (<0.1)
Hypoaesthesia	1 (0.2)	1 (0.2)	0	0	1 (<0.1)	1 (<0.1)
Insomnia	0	2 (0.3)	0	2 (0.5)	0	4 (0.4)
Irritability	0	0	1 (0.3)	1 (0.2)	1 (<0.1)	1 (<0.1)
Malaise	0	0	1 (0.3)	0	1 (<0.1)	0
Sleep disorder	1 (0.2)	0	0	0	1 (<0.1)	0
Somnolence	2 (0.3)	2 (0.3)	6 (1.5)	3 (0.7)	8 (0.8)	5 (0.5)
Syncope	0	1 (0.2)	0	0	0	1 (<0.1)
Terminal insomnia	0	1 (0.2)	0	0	0	1 (<0.1)

Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0
Adverse events (AEs) are listed in alphabetical order by intensity and preferred term.

Source: Sponsor's Integrated Summary of Safety, Appendix 2.6.2.1, p.1

Phase 2/3 Long-term Safety Study in Subjects with Migraine (BHV-3500 10 mg IN, BHV3500-202)

A total of 600 subjects received at least one dose of BHV-3500 10 mg IN in BHV3500-202, which was the only dose evaluated in this study. Patients in the open-label extension could administer BHV-3500 no more than once per day, up to eight times per month. AEs categorized as potentially associated with drug abuse were observed in 45 (7.5%) treated subjects. The most frequent AEs associated with potential drug abuse was insomnia (n=16, 2.7% subjects), fatigue (N=15, 2.5% subjects) and somnolence (N=3, 0.5% subjects). There were no reports of euphoria.

There was no dedicated evaluation for dependence or withdrawal. An overdose was reported in one (0.2%) subject and was the only PT identified from the MedDRA SMQ of "Drug abuse, dependence and withdrawal." The subject administered two sprays in one calendar day with no reported significant clinical consequence.

Non-Pooled Phase 1 Studies

Additional studies were reviewed but were not pooled due to use of different formulations (e.g., oral tablets). AEs associated with abuse potential in all the non-pooled Phase 1 studies were reported in a total of 15 subjects out of 602 subjects in the non-pooled studies. Most of the reported AEs of interest were in BHV3500-106, an 8-week safety study of an oral BHV-3500 dose at 100 mg per day in healthy subjects where AEs associated with abuse potential were reported in ten subjects (2.7%) and included fatigue (n=3, 0.8%), somnolence (n=2, 0.5%), and one subject (0.3%) each for hypoaethesia,

lethargy, sedation, irritability and sleep disorder. The remaining five reported AEs across the non-pooled studies were somnolence. No reports of euphoria were reported.

Conclusions:

The abuse-related safety profile of BHV-3500 (Zavegepant) is consistent with other CGRP antagonists and did not reveal any evidence of abuse liability in the preclinical or clinical program. No evidence of a dose-response for abuse-related AEs was identified. The drug product is therefore not recommended for any control status under the CSA. It is further recommended that prescribing information for BHV-3500 omit section 9 Drug Abuse and Dependence from PLR format product labeling.

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/

STEVEN A GALATI
12/21/2022 01:15:56 PM

JOSHUA M LLOYD
12/21/2022 03:30:37 PM

DOMINIC CHIAPPERINO
12/21/2022 10:26:01 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	October 6, 2022
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 216386
Product Name and Strength:	Zavzpret (zavegepant) nasal spray, 10 mg
Applicant/Sponsor Name:	Biohaven Pharmaceutical Holding Company, Ltd. (Biohaven)
OSE RCM #:	2022-501-1
DMEPA 2 Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

Biohaven submitted revised professional sample and trade container labels and carton labeling received on September 19, 2022 for Zavzpret (zavegepant) nasal spray. The Division of Neurology 2 (DN 2) requested that we review the revised professional sample and trade container labels and carton labeling for Zavzpret (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 ASSESSMENT AND CONCLUSION

We note that the expiration date format is not represented on the professional sample and trade container labels and carton labeling per our recommendation. However, per the Applicant's response to the Agency's recommendation (see Appendix A) they state that the expiration date will be in the format "YYYY-MM" where all characters will be numerical. Additionally, the Applicant included in their response to our recommendations the following responses: 1) the prominence of the strength "10 mg" and dosage form "nasal spray" were increased; 2) the statement (b) (4) was removed; and 3) the statement "Do not test spray, prime or press the plunger before use" was bolded. Lastly, the

[a] Weitzman B. Label and Labeling Review for Zavzpret (NDA 216386). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 JUL 27. RCM No.: 2022-501.

Applicant further states in their response that minor changes were made to the container labels and carton labeling (e.g., size of the 1-count carton size is slightly smaller). We note that these minor changes do not impact the content of the container labels or carton labeling.

The Applicant implemented all of our recommendations. As such, we find the revised professional sample and trade container labels and carton labeling acceptable from a medication error perspective and we have no additional recommendations at this time.

APPENDIX A. LABEL AND LABELING AND COVER LETTER

A.1. List of Label and Labeling and Response to Agency's Recommendations Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Zavzpret labels and labeling, and cover letter submitted by Biogen Inc. on September 19, 2022.

- Response to the Agency's recommendations available from docuBridge via: \\CDSESUB1\EVSPROD\nda216386\0015\m1\us\resp-to-fda-carton-20aug2022.pdf
- Commercial Presentation
  - Container label (device label)
  - Blister labeling (foil backing)
  - Carton labeling (6 count)
- Professional Sample Presentation
  - Container label (device label)
  - Blister labeling (foil backing)
  - Carton labeling (1 count)

Excerpt from Response to our Recommendations:

Container Labels, Blister Labeling (foil backing) and Carton Labeling (Trade and Professional Sample)

FDA Question 1

Provide more information regarding the expiration format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. 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

Biohaven Response to Question 1

Human-readable expiration date will be printed in MM/YYYY (e.g., 09/2022) format. All characters will be numerical, no alphabetical characters will be used.

FDA Question 2

To increase readability, we recommend increasing the prominence/size of the expression of strength "10 mg" and dosage form "nasal spray." If more space is needed for this important information, consider decreasing the size of the logo to increase the white space and improve readability.

Biohaven Response to Question 2

We have increased the prominence of "10 mg" and "nasal spray" by increasing the font size and white space. Due to the smaller size of the device label, we removed the branding element to allow for space to increase the font size on this component.

FDA Question 3

We recommend increasing the prominence of the statement "Do not test spray, prime or press the plunger before use" by bolding the entire statement and/or increasing the font size as space allows.

Biohaven Response to Question 3

The entire statement is now bold.

Blister Labeling (foil backing) and Carton Labeling (Trade and Professional Sample)

FDA Question 1

We recommend removing the statement [redacted] (b) (4) *from the blister and carton labeling.*

Biohaven Response to Question 1

The requested change has been made.

Other Labeling Modifications from the Sponsor

The Sponsor would like to make FDA aware of other changes being proposed and reflected on the revised artwork.

- The size of the 1-count carton size is slightly smaller. The height was reduced for better functioning.
- [redacted] (b) (4) have been removed on all components.
- The device label front was revised per the printing vendor to add a part number. Due to this addition, the [redacted] (b) (4) [redacted] (b) (4) was removed.
- The [redacted] (b) (4) was removed and replaced with a part number, per the printing vendor.

2 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

---

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/

BEVERLY WEITZMAN
10/06/2022 08:36:27 AM

STEPHANIE L DEGRAW
10/06/2022 09:56:17 AM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 216386
Submission Number	001 (New NDA)
Submission Date	3/9/2022
Date Consult Received	4/11/2022
Drug Name	Zavegepant
Indication	Acute Treatment of Migraine
Therapeutic Dose	10 mg (Intranasal)
Clinical Division	DN2
Protocol Review	(Link)

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

This review responds to your consult dated 4/11/2022 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review under IND-134120 dated 03/02/2020 in DARRTS (link);
- Sponsor's statistical analysis plan # BHV3500-101 (SN0001; link);
- Sponsor's statistical analysis plan # BHV3500-102 (SN0001; link);
- Sponsor's statistical analysis plan # BHV3500-101 and -102 (SN0001; link);
- Sponsor's clinical study report # BHV3500-101 and -102 (SN0001; link);
- Investigator's brochure ver. 5.0 (SN0001; link);
- Summary of clinical Safety (SDN0001; link); and
- Highlights of clinical pharmacology and cardiac safety (SN0001; link).

1 SUMMARY

No significant QTcF prolongation effect of zavegepant was detected in this QT assessment of ECGs collected in single ascending dose (SAD) and multiple ascending dose (MAD) studies (E14 Q&A 5.1).

The effect of zavegepant was evaluated in Studies BHV3500-101 and BHV3500-102 which are randomized, double-blind, placebo-controlled studies with SAD and MAD designs, respectively. The highest dose evaluated was 40 mg (20 mg × 2 sprays) intranasal (IN) administration which offers ~4-fold margin over the maximum therapeutic exposures (Cmax: ~13.4 ng/mL) associated with the proposed dosing regimen. This dose also covers two times the worst-case exposure scenario (in moderate hepatic impairment and subjects on concomitant administration with OATP1B3 and NTCP inhibitors; Section 0) and therefore supports waiving the requirement for inclusion of a positive control. Data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that zavegepant is associated with significant QTc prolonging effect (refer to Section 4.5)

– see Table 1. These findings are further supported by the available nonclinical data that showed a low risk for QT prolongation by direct inhibition of the hERG current at therapeutic exposure (hERG safety margin; >1800*x*). Similarly, no QTc prolongations were observed at exposures exceeded the high clinical exposure in the monkey studies (Section 3.1.2). In addition, the by-time analysis also indicated lack of dose-response (Section 4.3).

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

ECG Parameter	**Treatment**	**Concentration** (ng/mL)	**ΔΔQTcF** (msec)	**90% CI** (msec)
QTc	Zavegepant 40 mg QD	47.7	-1.7	(-4.2 to 0.9)

For further details of the FDA analysis, please see Section 4.

The reviewers observed elevated QT interval in the 5 mg dosing cohort on Day 14 without significant differences between the placebo and the higher 2 dosing cohorts on Day 14. The reason for this observation was unknown. The sponsor claimed that the observed QT prolongation is likely due to random variability as this effect was not observed on Day 1 for the 5 mg cohort as well as other higher dosing groups (Section 0). The reviewers' sensitivity analysis using complete dataset as well as the partial dataset (excluding the 5 mg dosing cohort including its placebo group) were consistent with the conclusions derived from the primary analysis (Section 4.5). Furthermore, the non-clinical data indicates that zavegepant has a low risk for QT prolongation by direct inhibition of the hERG current and no QTc prolongation was observed at exposures exceeded the high clinical exposure in the monkey studies (Section 3.1.2).

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN001 (link) from the CSS-IRT. Our changes are highlighted (*addition*, ~~*deletion*~~). Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At a dose~~s up to~~ 4 times the maximum approved recommended daily dose, <Tradename> does not prolong the QT interval to any clinically relevant extent.

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

Biohaven Pharmaceuticals, Inc. (Biohaven) is developing zavegepant as a nasal solution administered as an IN spray for the acute treatment of migraine. Zavegepant (BHV-3500; formerly BMS-742413 or vazegepant; MW 675.26 g/mol; HCl salt) is a calcitonin gene related peptide receptor antagonist. The IN formulation of zavegepant is comprised of BHV-3500 (free base) at (b) (4) mg/mL in a solution containing (b) (4) and dextrose at pH 6.0 and the product is delivered using a single-dose device (b) (4) A single dose of 10 mg is the maximum proposed dose in a 24-hour period.

Throughout the drug development program, the maximum doses of zavegepant evaluated included IN administration of single doses of 40 mg, as daily multiple doses of 20 mg dose for up to 14 days, as daily multiple doses up to 8 days at 40 mg, and a 40 mg dose in alternate nostrils (2 × 20 mg) on a single day. The highest exposures of zavegepant following a single dose and multiple doses were achieved with 20 mg (10 mg sprays in each nostril) and 40 mg (20 mg × 2 sprays), respectively: Cmax = 33.95 ng/mL (single dose) and 48.24 ng/mL (multiple dose). No maximum tolerated dose was identified after administration up to 40 mg (20 mg × 2 sprays) IN single dose of zavegepant. Slightly less than dose-proportional increase in the exposure following single IN dose administration over the dose ranged from 1 mg to 40 mg. Following daily IN dosing of zavegepant, minimal accumulation (0.62 to 1.44) of zavegepant was observed at all doses tested.

Zavegepant is primarily metabolized by CYP3A4 and to a lesser extent by CYP2D6, in vitro. After single IV dose of 5 mg [^{14}C]-zavegepant, the parent compound (zavegepant) was the most prevalent (approximately 90%) circulating component in the human plasma and no major metabolites (i.e., > 10%) of zavegepant were detected in plasma. Zavegepant is majorly eliminated through feces with unchanged form as the major single component. Zavegepant is a substrate for OATP1B3 and NTCP transporters and a dedicated clinical drug interaction study (BHV3500-1111) using rifampin (OATP1B3 and NTCP inhibitor) showed an increase in the Cmax by 2.2-fold (24.12 ng/mL). A clinical drug interaction study evaluating the impact of 10 mg zavegepant exposures in moderate hepatic impairment individuals showed an increase in the Cmax by 1.2-fold. The increase in the exposures with rifampin (24.12 ng/mL) was considered as the expected high clinical exposure scenario for zavegepant. Zavegepant maximum exposure (48.24 ng/mL) observed in the multiple dose study with 2 × 20 mg dose provided a 2-fold difference in the exposure margin with the expected high clinical exposure scenario with zavegepant.

Zavegepant dose frequency adjustments are proposed by the sponsor in moderate hepatic impairment patients and patients taking concomitant medications that inhibit both OATP1B3 and NTCP (10 mg IN no more than once every 48 hours). An IR was sent to the sponsor on 06/01/2022 to provide simulations of the zavegepant exposures to steady

state with the proposed dose frequency adjustments (10 mg, no more than once every 48 hours). In response on 06/17/2022, the sponsor submitted the results from simulations performed using non-parametric superposition and population PK modeling. Using both the methods, the increase in the exposures with the proposed dosing regimen in moderate hepatic impairment subjects or subjects taking concomitant OATP1B3 and NTCP inhibitor were < 10%.

The sponsor characterized the risk of QT prolongation of zavegepant in SAD (Study # BHV3500-101) and MAD (Study # BHV3500-102) studies. The IRT received a consult request to review the assessment plan (IND # 134120). BHV3500-101 was a placebo-controlled, randomized, double-blind, sequential SAD study and BHV3500-102 was a placebo-controlled, randomized, double-blind, sequential MAD study. In SAD study, 9 dose cohorts of 0.1, 0.3, 1, 3, 5, 10, 20, 20 mg [2 × 10 mg sprays], and 40 mg [2 × 20 mg sprays] with 8 subjects per dose group randomized 6:2 to zavegepant and placebo were studied. The maximum Cmax was ~ 34 ng/mL, observed in the 2 × 10 mg dose group. In MAD study, the first 3 cohorts received 5 mg, 10 mg, 20 mg QD, respectively, for 14 days (n = 9/3 for zavegepant/placebo in each cohort) and cohort 4 received 2 sequential 20 mg zavegepant doses separated by 2 hours each day for 8 days (n = 9/3 for zavegepant/placebo). The maximum Cmax was ~ 48.2 ng/mL, observed in the 2 × 20 mg dose group on day 1, covering 1.7*x* high clinical exposure. Both studies showed no HR effect. The by-time analysis showed the upper bound of 90% CI of ΔΔQTcF < 10 msec for all dose groups except for the 5 mg on day 14 in the MAD study. Concentration-QTc analysis showed negative slopes. However, the sponsor proposed dose adjustment for the identified high clinical exposure scenario. Thus, the exposures (Cmax) at the supratherapeutic doses studied (i.e., 40 mg single dose and multiple doses) in these QT studies are expected to offer ~4-fold margin over zavegepant therapeutic exposures (10 mg) and ~2-fold margin over the intrinsic (moderate hepatic impairment) and extrinsic (rifampin DDI) factors that increase zavegepant exposure. Individual and pooled concentration QT analysis of the studies was conducted.

The reviewers observed elevated QT prolongation at 5 mg dosing cohort on Day 14 without significant differences between the placebo group for 5 mg dosing cohort and the other 2 dosing cohorts on Day 14. The reason for this observation was unclear. The sponsor claimed that the observed QT prolongation is likely due to random variability as this effect was not observed on Day 1 for 5 mg cohort as well as other higher dosing groups. For this purpose, the reviewers performed analyses in the complete dataset, as well as the dataset excluding the 5 mg dose cohort (excluding the entire cohort, which includes placebo) for sensitivity analysis. In addition, non-clinical and safety findings were summarized to evaluate totality of evidence.

3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to the sponsor's highlights of clinical pharmacology and clinical safety.

Overall, zavegepant does not show significant cardiovascular effects in the in vitro assays for human ether-a-go-go related gene (hERG), sodium channel or Purkinje fibers up to maximum test concentrations of 30 μM, or in vivo in telemetered monkeys.

In Vitro: In a hERG assay, zavegepant was tested at concentrations of 10 and 30 μM (Study DT05135). Zavegepant had minimal effects on the hERG potassium currents which were inhibited by 9.5 ± 3.2% (Mean ± SEM, n = 4) and 21.7 ± 3.4% (Mean ± SEM, n = 4) at 10 and 30 μM, respectively. Cardiac sodium currents with 30 μM zavegepant were inhibited by 5.9 ± 2.4% and 8.7 ± 1.1% (Mean ± SEM, n = 3) at 1 and 4 Hz stimulation frequency, respectively. In the rabbit Purkinje fiber assay, zavegepant did not have any significant effects on any of the action potential parameters measured up to a maximum test concentration of 30 μM.

Monkey: A GLP cardiovascular safety pharmacology study was conducted in telemetered cynomolgus monkeys (Study 1016-3833) with the objectives of the study to assess the potential pharmacological effect of zavegepant on the cardiovascular system (electrocardiogram and arterial blood pressure) following a single SC injection. There were no mortalities during the study. Except for slight non-adverse local reactions on and/or around the dosing sites, there were no clinical signs considered related to SC administration of zavegepant. Cardiovascular data did not show any effect on ECG or blood pressure that could be attributed to zavegepant when administered SC up to 37.5 mg/kg (approximately 14,000 ng/mL to 16,000 ng/mL, or 22 μM to 25 μM). Based on the results obtained under the conditions of this study, the NOEL of zavegepant on cardiovascular function was 37.5 mg/kg (highest tested dose)

Reviewer's assessment: *The sponsor evaluated the effects of BMS-742413 (zavegepant) on hERG current, a surrogate for IKr that mediate membrane potential repolarization in cardiac myocytes. The study report (DT05135; link) describes the potential effects of zavegepant on the hERG current in HEK293 cells. The hERG current was assessed at room temperature (25°C) using a step-step voltage protocol (from a holding potential of -80 mv to a depolarizing pulse of 20 mV for 2 seconds, followed by a repolarizing pulse to -65 mV for 3 seconds) that is different from the recommended hERG current protocol by the FDA (link). The reviewer does not expect protocol differences to impact hERG current pharmacology. No positive control drugs were tested in the study to assess the sensitivity of the assay. A full blocker (e.g., E-4031 at 1 μM) was not added to the end of the experiment to assess the non-hERG currents evoked by the voltage protocol. Drug concentrations were not verified in the study.*

Zavegepant inhibited the hERG currents by 9.5± 3.2 %, 21.7 ± 3.4% at 10 and 30 μM, respectively. The IC50 for the inhibitory effect of zavegepant on hERG current is greater than 30 μM. The hERG safety margins of zavegepant on hERG current are summarized below:

Table 2 Safety margin of zavegepant on hERG Current

	Cmax (ng/mL)	*Protein Binding*	*Free Cmax (ng/mL)*	*hERG IC50 (μM)*	*Mol Weight (g/mol)*	*Safety Margin (Ratio)*
zavegepant	*29*	*63%*	*10.73*	*> 30*	*675.26*	*>1888x*

Cmax:13.4 ng/mL at 10 mg intranasal. The intrinsic/extrinsic factor that increases Cmax the most is co-administration with OATP1B3 and NTCP inhibitor, which resulted in a 2.2-fold increase in Cmax (~29 ng/mL).

The sponsor also evaluated the effects of zavegepant on cardiac sodium current in HEK293 cells in the same study report (DT05135; link). The Nav1.5 current was assessed at room temperature, using a step voltage protocol from a holding potential of -90 mV to 20 mV for 60 ms. At 30 μM, BMS-742413 inhibited the cardiac sodium currents by 5.9 ± 2.4% and 8.7 ± 1.1% (Mean ± SEM, n = 3) at 1 and 4 Hz stimulation frequency, respectively. No positive control was used in the Nav1.5 assay. Drug concentration was not confirmed in the study.

The in vivo monkey study (1016-3833) assessed the potential effects of zavegepant on ECG parameters following single subcutaneous doses at 5, 15 and 37.5 mg/kg to male cynomolgus monkeys instrumented with telemetry devices using a crossover Latin square design. Cardiovascular function parameters were reported approximately every 15 minutes for a period of 1 hour prior to dosing, every 15 minutes for 4 hours post-dosing and every hour for the remainder of the 24 hours post-dosing. No blood samples were collected for TK study. There were no zavegepant -related QTc, QRS changes at dose up to 37.5 mg/kg. The sponsor predicated the exposure would be 14,000 ng/mL to 16,000 ng/mL (~ 500x high clinical exposure) at dose of 37.5 mg/kg. No positive drugs were used in the study.

Another in vivo study (DS05143) evaluated the potential effects of zavegepant on ECG parameters following single subcutaneous dose (3 mg/kg) in 6 monkeys. ECG parameters (RR, PR, QRS, and QT intervals) were collected from all instrumented animals for approximate 1-hour period prior to treatment and continuously for approximately 20.5 hours following dose. No zavegepant-related changes in PR interval, QRS duration and QT interval were observed. Subcutaneous administration of BMS-742413 (3 mg/kg) resulted in 4-hour post-dose exposures of 161.2 and 201.7 ng/mL in males and females, respectively. The exposure exceeded (5.5~6.9 x) the anticipated high clinical exposure in humans (29 ng/mL). No positive drugs were used in the study.

In summary, while the hERG assay showed deviations (e.g., room temperature, no drug concentration verification, and no positive controls) from the best practice recommendations for an in vitro assay according to the new ICH S7B Q&A 2.1, the results show that zavegepant has a low risk for QT prolongation by direct inhibition of the hERG current at therapeutic exposure. The limitations of the assay will not substantially impact the large hERG safety margin (i.e., > 1888 x).

No QTc prolongations were observed at exposures exceeded the high clinical exposure in the monkey studies.

The QT prolongation in the 5 mg dose cohort on day 14 in study BHV3500-102 cannot be explained by the non-clinical data.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for zavegepant was based on exposure-response analysis, please see Section 3.2.3 for additional details.

Reviewer's comment: *The data from cohort 1 of study BHV3500-102 is different from the rest of the cohorts in the study, since the elevation in ΔΔQTcF was only observed in the low 5 mg QD dose group on Day 14, but not on Day 1. Thus, main analyses from FDA reviewer were based on all data excluding 5 mg dose group and placebo from cohort 1. The analyses including 5 mg dose group are served as sensitivity analysis. Because the conclusions of main analysis and sensitivity analysis are consistent, only main analyses results are presented in the review report. Given the small sample size of each dose level, FDA reviewer used non-parametric statistics to summarize the data. The trend shown in by-time analysis from reviewer's analysis is similar to the trend shown in sponsor's by-time analysis.*

3.2.1.1 Assay Sensitivity

Not Applicable.

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., >500 msec or >60 msec over baseline), HR (<45 or >100 beats/min), PR (>220 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *FDA reviewer's analysis results are the same with sponsor's analysis results. Please see Section 4.4 for details.*

3.2.3 Exposure-Response Analysis

The sponsor performed PK/PD analysis using the model recommended in the white paper to explore the relationship between plasma concentrations of zavegepant and ΔΔQTcF (placebo-corrected change from baseline in QTcF) using a linear mixed-effects model with a treatment effect specific intercept approach on all subjects in the analysis data set for cardiac assessment. The sponsor analysis indicates a slight negative slope of -0.044 msec/ng/mL (90% CI: -0.1231, 0.0346 msec/ng/mL) between zavegepant plasma concentrations and ΔΔQTcF. The model predicted ΔΔQTcF (upper 90% confidence interval) values of -0.81 (2.38) msec at the mean peak concentrations on Day 14 for the 20 mg zavegepant dose (geomean Cmax ~40.9 ng/mL) following multiple doses. Similarly, the model predicted ΔΔQTcF (upper 90% confidence interval) values of -0.01 (1.83) msec at the mean peak concentrations on Day 8 after dosing with the 40 mg (2 × 20 mg sprays; geomean Cmax ~23.0 ng/mL) following multiple doses. The results of the sponsor's analysis suggest an absence of significant QTc prolongation at the proposed therapeutic dose (i.e., 10 mg intra-nasal daily)

Reviewer's comment: *Although there are some numerical differences, the results of the reviewer's analysis agreed with the sponsor's conclusion. Please see Section 4.5 for additional details.*

3.2.4 Safety Analysis

In study BHV3500-101, there were no potential QT prolongation/TdP-related AEs. No clinically meaningful results in vital signs or ECGs were identified in this study.

In study BHV3500-102, one subject in the pooled zavegepant group (1.8%) had a severe syncope AE and one subject in the placebo group (6.3%) had a moderate presyncope AE. No clinically meaningful changes from baseline in vital signs, ECGs, or S-STS were identified in this study.

Reviewer's comment: *Please see Section 4.6 for the reviewer's safety assessment.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable. A large increase in heart rate (i.e., median>10 beats/min) was only observed in Zavegepant 20 mg QD dose group (9 subjects in 20 mg QD group and 3 subjects in placebo were used in the calculation) on Day 1 from study BHV3500-102. However, this increase in HR was observed at one single timepoint potentially due to small sample size. No large increases or decreases in heart rate for other treatment groups were observed (Section 4.3.2).

4.2 ECG ASSESSMENTS

Cohort 1 of 5 mg dose group and placebo was excluded from exposure-response analysis (Section 4.5). Thus, the subjects from study BHV3500-102 except in Cohort 1 of 5 mg dose group and placebo and all subjects in study BHV3500-101 are included in the following analyses: by-time analysis, exposure-response analysis and category analysis.

4.2.1 Overall Quality

ECG acquisition and interpretation in these two studies appear acceptable.

4.2.2 QT Bias Assessment

Not applicable.

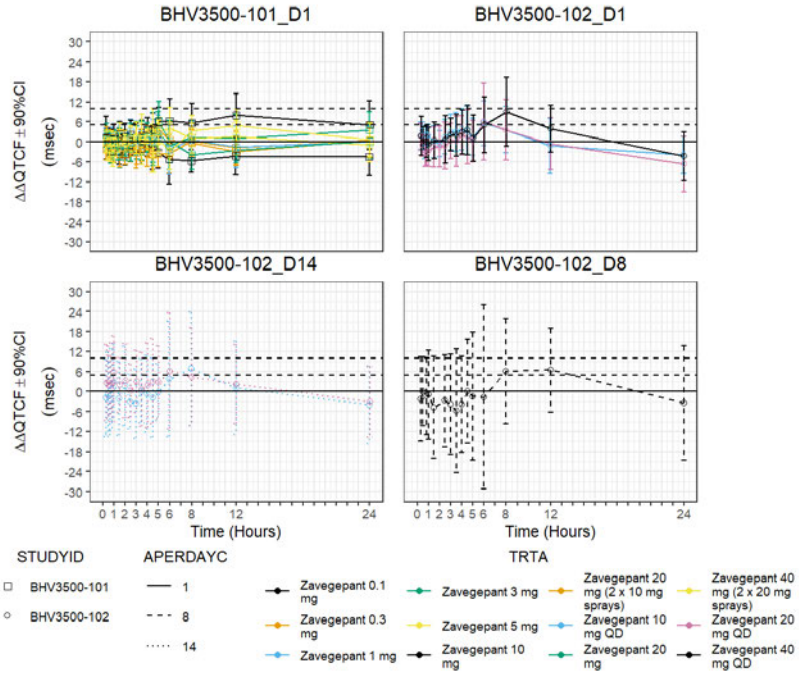
4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG except the subjects in cohort 1 of study BHV3500-102. The statistical reviewer evaluated the ΔQTcF effect using descriptive nonparametric statistics.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups.

Figure 1: Median and 90% CI of ΔΔQTcF Time-course (unadjusted CIs).



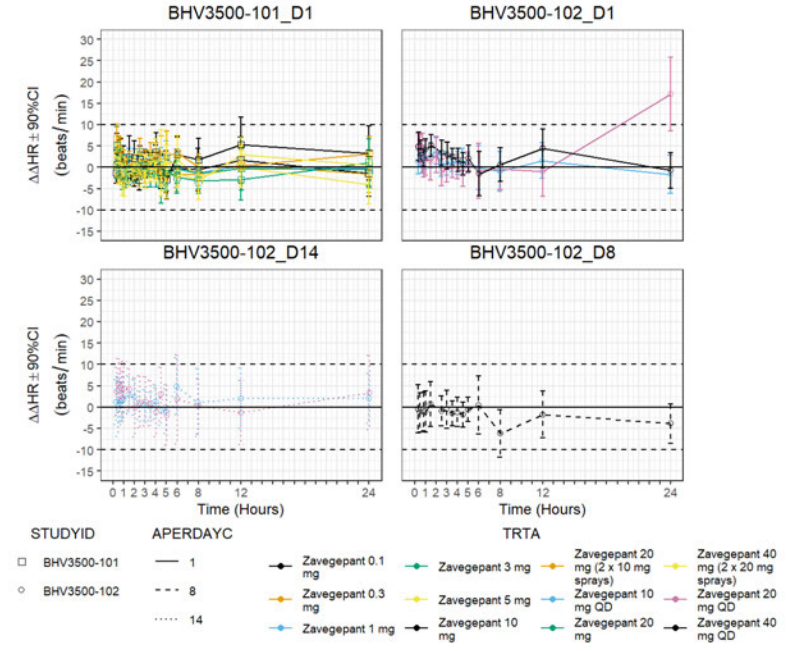
4.3.1.1 Assay Sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

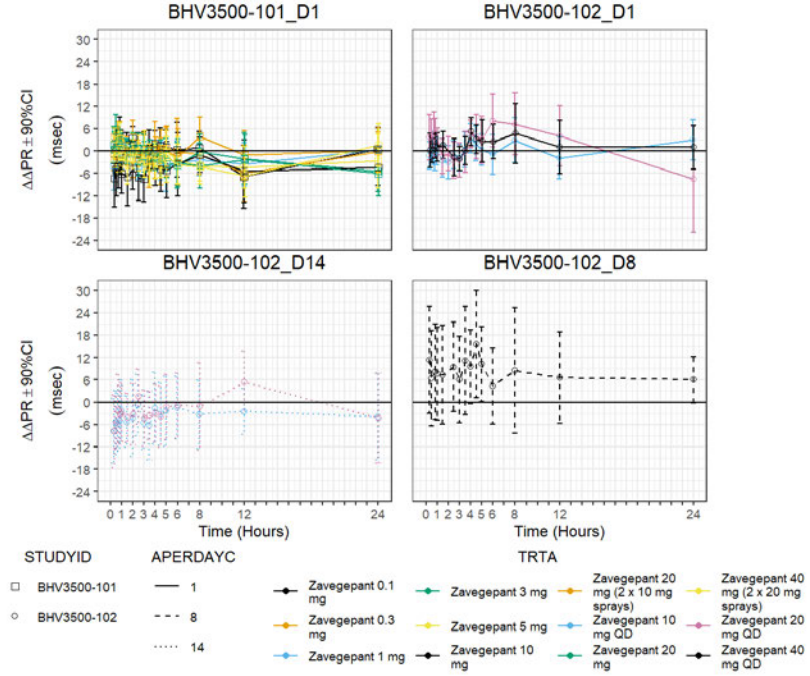
Figure 2: Median and 90% CI of ΔΔHR Time-course



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

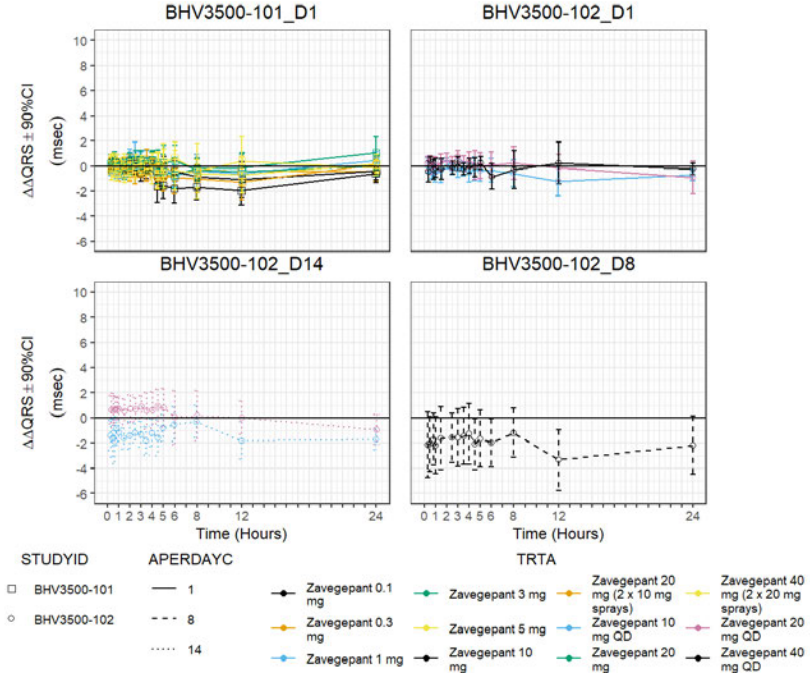
Figure 3: Median and 90% CI of ΔΔPR Time-course



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Median and 90% CI of ΔΔQRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

There were no subjects having observed QTcF above 480 msec or change from baseline above 60 msec after receiving Zavegepant.

4.4.2 HR

There were no subjects having observed maximum HR above 100 beats/min.

4.4.3 PR

None of the subjects experienced PR >220 msec in any of the treatment groups.

4.4.4 QRS

None of the subjects experienced QRS >120 msec and 25% increase over baseline in any of the treatment groups.

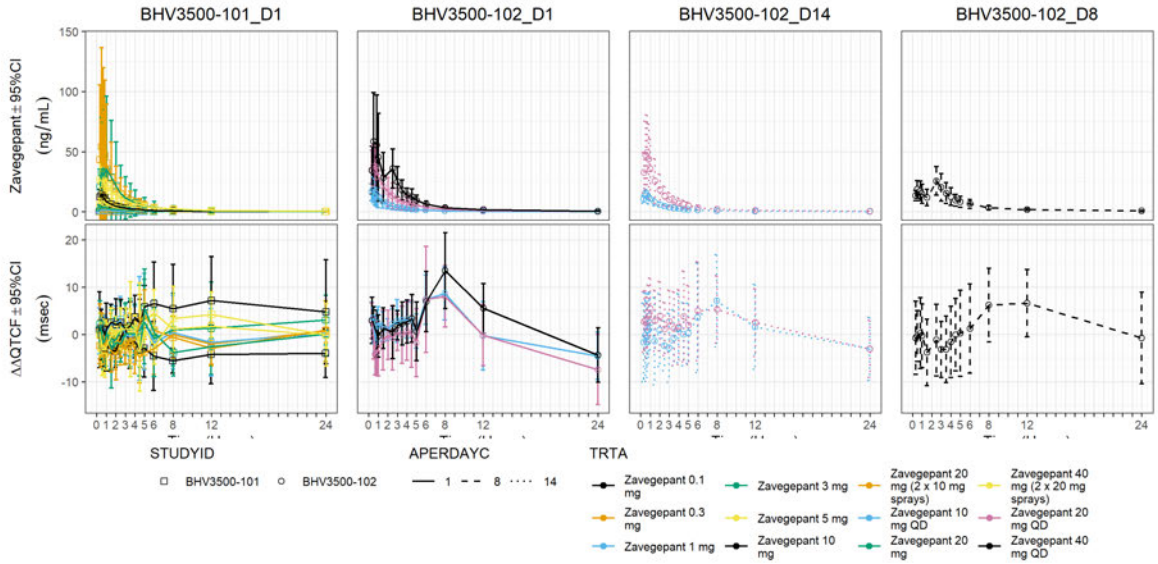
4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of this analysis was to assess the relationship between zavegepant plasma concentration and ΔΔQTcF. Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK. As indicated earlier in Section 3.2.1, the primary exposure-response analysis was based on all data excluding 5 mg dose group and placebo from cohort 1 in study BHV3500-102 and the analyses including 5 mg dose group served as sensitivity analysis.

Prior to evaluating the relationship between zavegepant concentration and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: absence of - 1) significant changes in heart rate (more than a 10-bpm increase or decrease in mean HR); 2) delay between zavegepant concentration and ΔΔQTcF and 3) a non-linear relationship.

Figure 2 shows the time-course of ΔΔHR, with an absence of significant ΔΔHR changes, except for 20 mg QD dose group on Day 1 in study BHV3500-102 (refer to Section 4.3.2 for more details). Figure 5 offers an evaluation of the relationship between time-course of zavegepant concentration and changes in ΔΔQTcF.

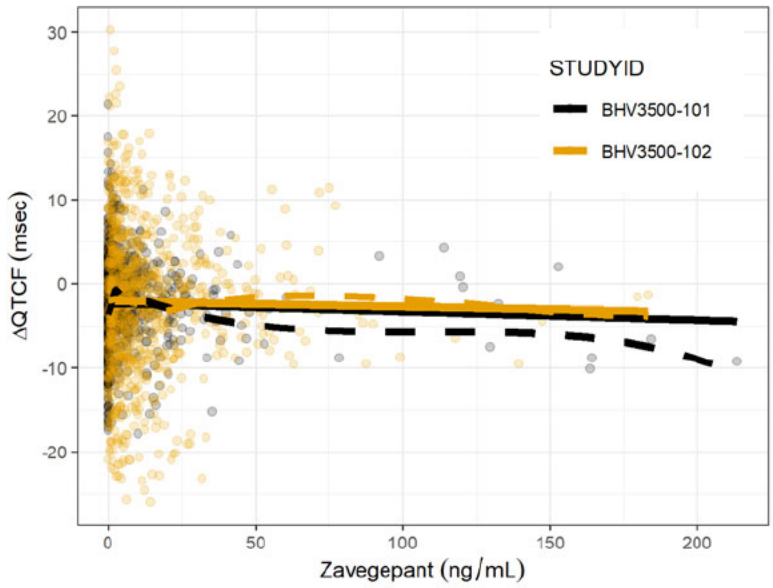
Figure 5: Time-course of Zavegepant Concentration (top) and QTcF (bottom)[1]



There was a delay between the time to reach maximum zavegepant plasma concentration (median Tmax range - 0.33 to 2.5 h) and maximum ΔΔQTcF (range - 0.3 to 24 h). The mechanism for delayed ΔΔQTcF response is not known. However, there was no apparent dose-response relationship, i.e., despite the 40 mg dose resulting in significantly higher concentrations than the lower dose groups (0.3 to 20 mg), the QT effects are similar between all the doses (Figure 5; bottom panel). Therefore, the delay in the QTc changes were not considered to be clinically significant.

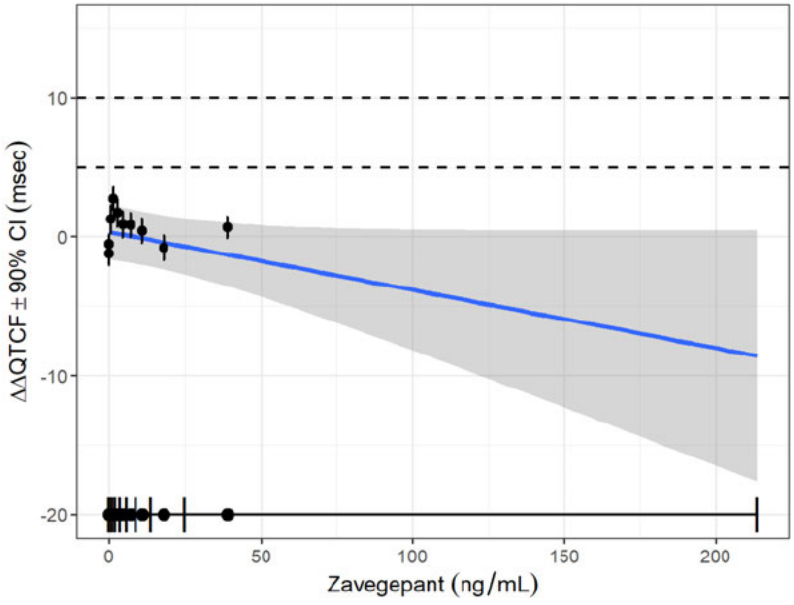
[1] ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



After confirming the absence of significant heart rate changes and delayed QTc changes, the relationship between zavegepant plasma concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between zavegepant concentration and ΔQTcF and supports the use of a linear model.

Figure 7: Goodness-of-fit Plot for QTcF



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table .

Table 3: Predictions from Concentration-QTcF Model

Actual Treatment	Zavegepant (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
Zavegepant 10 mg QD	16.3	-0.3	(-2.3 to 1.6)
Zavegepant 40 mg QD	47.7	-1.7	(-4.2 to 0.9)

The results from the sensitivity analysis indicated that there were no significant differences in the estimated key model parameters (intercept and slope) compared to the primary analysis (data not shown). Therefore, it was concluded that the exclusion of 5 mg dose and placebo from cohort 1 of BHV3500-102 study from the primary analysis did not have any significant effect on the evaluation of zavegepant QTcF prolongation.

4.5.1 Assay Sensitivity

Not applicable.

4.6 SAFETY ASSESSMENTS

There was no concerning imbalance in potential TdP/QT prolongation-related adverse events.

In study BHV3500-102, one subject (BHV3500-102-(b) (6)) in the pooled zavegepant group (1.8%) had a severe syncope AE. No narratives were provided for this event by the sponsor. The subject was a 48-year-old white male, randomized to cohort 6 (2 × 20 mg) where he received one 20 mg zavegepant in each nostril on (b) (6) at 7:38 (right) and 7:43 (left) respectively. At 7:45, he experienced mild dysgeusia and moderate dizziness and at 7:55 he experienced severe syncope. None of the AEs were SAEs. The dysgeusia/dizziness/syncope were considered probably/possibly/remotely related to the study drug by the investigator. All events were resolved in 2 hours. Continuous Holter ECGs were not performed in cohort 6 and subject (b) (6) only had pre-dose ECG with normal QTcF (399 msec). All labs were within normal range except for slightly elevated monocytes/leukocytes at both baseline and day 2. Medical history included allergy to animal and tonsillectomy. Concomitant medication included ibuprofen.

Reviewer's comment: There is no information showing the relation between this severe syncope to QT prolongation.

In the single-dose studies in subjects with migraine (BHV3500-301 and -201), 1023 and 1056 subjects received zavegepant 10 mg IN and placebo, respectively. On-treatment ECG QT prolongation AEs were reported in 2 (0.2%) subjects in the zavegepant group and 1 (< 0.1%) subject in the placebo group in the safety analysis set of the single-dose studies in subjects with migraine (zavegepant 10 mg IN).

- Subject BHV3500-201-(b) (6) (ECG QT prolonged): A 38-year-old white female in the BHV3500-201 study, who was randomized to the zavegepant 10 mg group on (b) (6) had an event of QT interval prolonged QTcF 486ms (verbatim term) that was mild in intensity at the EOT visit (Study Day 15, (b) (6)) after taking the single dose of zavegepant 10 mg on Study Day 10 (b) (6) No action was taken with zavegepant. The event was considered unlikely to be related to study drug by the investigator. The medical history included anxiety. The central ECG vendor's interpretation of the subject's ECG results at the Screening visit reported QT/QTcF of

416/426 msec, and these results were interpreted as normal. The ECG results at the EOT visit (Study Day 15, (b) (6)) reported QT/QTcF of 386/486 msec and were interpreted as abnormal, with clinically significant prolonged QT interval (QTcF > 450 msec), aberrant supraventricular conduction, and premature atrial complexes; the ECG also noted sinus rhythm and normal T wave morphology. Additionally, the ECG results reported anteroseptal myocardial infarction - old (age indeterminate).

Review of the ECG results at the EOT visit (Study Day 15, (b) (6)) by the Sponsor's cardiac electrophysiologist found a fairly irregular sinus rhythm with multiple aberrantly conducted atrial premature contractions (Ashman beats). This level of irregularity makes calculating a corrected QT problematic. QT was measured by the cardiac electrophysiologist following long and short cycles at 360 and 440 msec. Based upon an average rate of 68 bpm, this would yield a QTcF of 375 and 459 msec, respectively. Of note, the ECG machine's results reported QT as 386 msec and HR as 68 bpm, with QTcF reported as 486 msec. A manual check of this calculation yields a QTcF of 402 msec, not 486 msec, based upon a HR of 68 bpm. The ULN of the QTcF for females is 470 msec, which was also the protocol-defined exclusion value for QTcF; none of the above overread values exceed this value. A review of the QRS morphology and R wave progression does not show interval change since the Screening visit ECG tracing. Specifically, the QRS morphology across the precordium for the sinus conducted beats were the same between the two ECG tracings; this does not support the diagnosis of an interval anteroseptal myocardial infarction. It seems probable that the aberrantly conducted complexes (Ashman beats) on the latter tracing may have led to a machine misinterpretation of anteroseptal myocardial infarction.

Reviewer's Comment: The prolongated QTcF occurred 5 days after the last dose of the study drug and was considered unlikely to be related to study drug by the investigator. The QTcF might not be calculated reliably due to the irregularity of sinus rhythm.

- Subject BHV3500-301 (b) (6) (ECG QT prolonged): A 62-year-old, Native Hawaiian or other Pacific Islander male in the BHV3500-301 study who was randomized to the zavegepant 10 mg group on (b) (6) had an event of ECG prolonged QT that was mild in intensity at the EOT visit (Study Day 36, (b) (6)) after taking the single dose of zavegepant 10 mg on Study Day 31 (b) (6) No action was taken with zavegepant as a result of the AE of ECG QT prolonged. The event was considered possibly related to study drug by the investigator. Ongoing medical history included asthma, hypercholesterolaemia, hypertension, and insomnia. The subject's ECG results at the Screening visit (Study Day -16, (b) (6)) reported QT/QTcF of 398/402 msec, and these results were interpreted as abnormal with a clinically nonsignificant finding of left ventricular hypertrophy; the ECG also noted sinus rhythm, normal T-wave morphology, and precordial lead misplaced. An overread by the Sponsor's cardiac electrophysiologist yielded QT/QTcF of 380/382 msec. The ECG results at the EOT visit (Study Day 36) reported QT/QTcF of 420/451 msec (HR 74 bpm), and was interpreted as abnormal with a clinically significant finding of prolonged QT interval (QTcF > 450 msec); the ECG also noted sinus rhythm, and normal T-wave morphology. The overread by the Sponsor's cardiac electrophysiologist yielded QT/QTcF of 400/429 msec. A QTcF calculation, based on the ECG machine's values (QT = 420 msec, HR 74 bpm), by the cardiac electrophysiologist yielded 450 msec, which is the ULN for QTcF in males.

Reviewer's Comment: The prolongated QTcF occurred 5 days after the last dose of the study drug. It was considered possibly related to study drug by the investigator. The cardiologist overread showed normal QTcF.

In the long-term open-label safety study in subjects with migraine (BHV3500-202) where 600 subjects received zavegepant 10 mg IN per calendar day as needed, up to 8 times per month for up to 52 weeks, on-treatment potential QT prolongation/seizure AEs were

reported in 3 (0.5%) subjects (PTs of syncope in 2 subjects, and ECG QT prolonged in 1 subject).

Subject Identifier (PID) (Sex/Age/Race)	Preferred Term	Verbatim Term	Intensity/ Relatedness	Duration of PT (days)	Seriousness	Action Taken with Study Drug
BHV3500-202-(b) (6) (Female/50 years old/ white)	Syncope	Syncopal episode	Moderate/ not related	1	Not serious	Dose not changed
BHV3500-202-(b) (6) (Male/28 years old/ white)	Syncope	Near syncopal episode	Moderate/ unlikely related	1	Not serious	Dose not changed
	Syncope[a]	Near syncopal episode	Moderate/ not related	1	Not serious	Dose not changed
BHV3500-202-(b) (6) (Female/35 years old/ white)	ECG QT prolonged	QT prolongation	Mild/possibly related	15	Not serious	Dose not changed

[a] The event occurred 2 days after the subject's last dose of study drug.

- Subject BHV3500-(b) (6) (Syncope): On (b) (6) (Study Day 36), the subject experienced syncope (verbatim term: syncopal episode) of moderate intensity that resolved on the same date. In the 30 days prior to and including the date of the AE, the subject reported taking 6 doses of zavegepant, with the last dose taken on the date of the event ((b) (6) timing of dose in relation to AE was not recorded). No treatment was reported for the event, and no action was taken with zavegepant as a result of the AE of syncope.

  On (b) (6) (Study Day 29), at the Week 4 visit, 7 days prior to the AE of syncope, the subject's hematology panel was notable for low hemoglobin (9.9 g/dL), low hematocrit (34.5%), and low RBC count (3.77 × 1012/L). On that same date, an AE of anaemia of moderate intensity was reported. The subject's medical history was notable for iron deficiency anemia ((b) (6) to ongoing) and heavy menstrual bleeding ((b) (6) to ongoing). Prior treatment for the subject's iron deficiency anemia included 510 mg of intravenous iron (ferumoxytol) every 3 months; however, infusion frequency was changed to weekly as treatment for the AE of anaemia. This treatment medication remained ongoing, as the AE was considered ongoing at the end of the study. No action was taken with zavegepant as a result of the AE of anaemia.

  From Screening (b) (6) through the Week 4 visit (b) (6) the subject's blood pressure ranged from 103/68 mmHg to 131/79 mmHg, and heart rate ranged from 63 to 71 beats per minute. From the Week 8 (b) (6) through the Week 2 Follow-up (b) (6) visits, the subject's blood pressure ranged from 100/64 mmHg to 126/67 mmHg, and heart rate ranged from 67 to 78 beats per minute. An electrocardiogram (ECG) at Screening was considered abnormal and possibly clinically significant: sinus rhythm and T wave normal. An ECG at the Week 4 visit was considered normal.

  A review of the 4 ECGs obtained from this subject during the study was performed by a cardiac electrophysiologist employed by the sponsor. All 4 tracings revealed normal sinus rhythm, with normal features and no interval changes over the 4-month period (b) (6) (b) (6) The QTcF on the tracing from (b) (6) was 452 msec (normal for females, < 470 msec). The QTcF on the tracing from (b) (6) was 444 msec; on (b) (6) it was 442 msec, on (b) (6) (b) (6) it was 453 msec. The QTcF thus varied within the normal range by 11 msec: from 442 msec to 453 msec over a period of 4 months. This is considered a normal finding. No other abnormalities were noted during this review.

  The subject experienced worsening of generalized anxiety and worsening of depression on (b) (6) (b) (6) (Study Day 65). Zavegepant was permanently discontinued due to the AE of anxiety, with the last dose taken on (b) (6) The subject was withdrawn from the study due to the AE of anxiety, with the last study visit on (b) (6)

Reviewer's Comment: All ECGs obtained during the study for this subject were normal. An ECG was not performed on the day of the syncope event and the QTcF was 444 msec one week prior to the event. The syncope event could be related to the ongoing anemia.

- Subject BHV3500-202 (b) (6) (Syncope): Figure 8 showed a timeline of AEs and QTcF for this subject. From (b) (6) (Study Day 2) to (b) (6) (Study Day 25), after each subsequent dose of zavegepant (6 doses in total), the subject reported disorientation of mild intensity. The AEs of disorientation were considered resolved on their respective date of onset. Zavegepant was not taken between AEs. No treatment was given and no action was taken with zavegepant as a result of any of these AEs. The subject continued in the study and continued taking zavegepant PRN for migraine.

  On (b) (6) (Study Day 96), the subject reported increasing severity of migraines of moderate intensity. In the 30 days prior to and including the onset date of the AE, the subject reported taking 11 doses of zavegepant, with the last dose taken on the date of the event (b) (6) No treatment was given for migraine other than zavegepant, and the AE was considered resolved on (b) (6) No action was taken with zavegepant. The subject continued in the study and continued taking zavegepant PRN for migraine. Between (b) (6) and (b) (6) the subject reported taking 12 doses of zavegepant. The investigator assessed the AE of migraine (moderate) as possibly related to zavegepant.

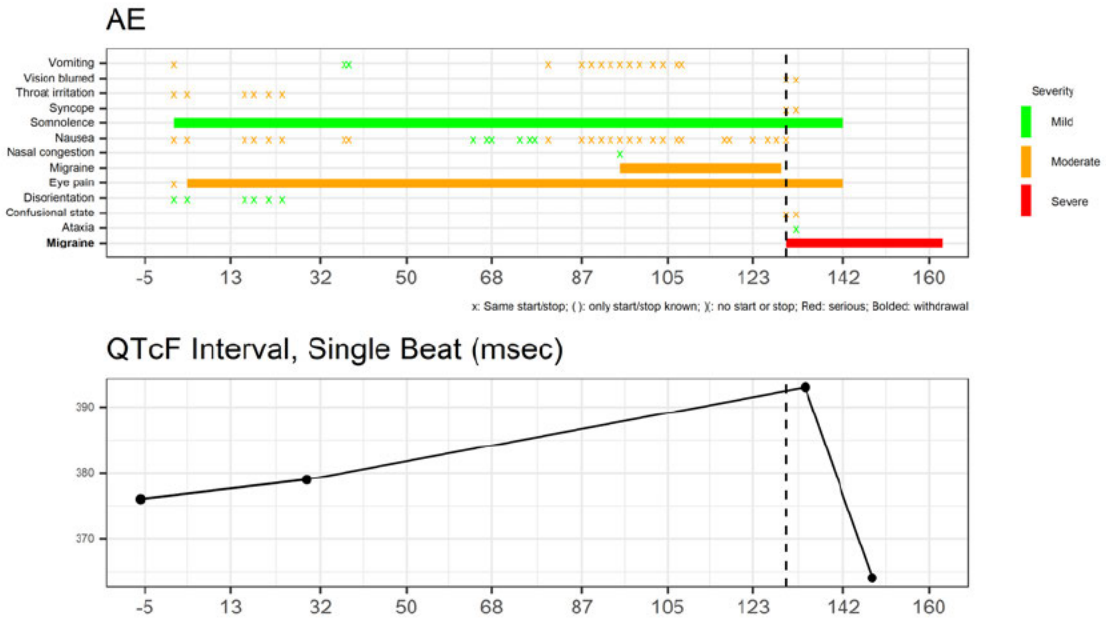
  On (b) (6) (Study Day 131), the subject reported worsening of migraine of severe intensity. In addition, the subject described having a near syncopal of moderate intensity and experienced confusion of moderate intensity. No treatment was given for any of these events. All of

  the AEs were considered resolved the same date as onset (b) (6) except for the AE of migraine (severe), which was considered resolved on (b) (6) Zavegepant was permanently discontinued due to the AE of migraine (severe), with the last dose taken on (b) (6)

  On (b) (6) (Study Day 133), the subject reported a near syncopal episode and confusion that were reported as AEs of syncope and confusional state, both of moderate intensity. Concurrently, the subject reported having blurred vision and ataxia that were reported as AEs of vision blurred of moderate intensity and ataxia of mild intensity. No treatment was given for any of these AEs, and all of the AEs were considered resolved on the same date as onset (b) (6) No action was taken with zavegepant as a result of the AEs of syncope and confusional state, or the concurrent AEs of vision blurred and ataxia, because zavegepant had already been discontinued (last dose (b) (6) (b) (6)) due to the AE of migraine (severe).

  From Screening (b) (6) through the Week 16 visit (b) (6) the subject's blood pressure ranged from 117/78 mmHg to 141/83 mmHg, and heart rate ranged from 73 to 108 beats per minute. An electrocardiogram (ECG) at Screening was considered abnormal with QT/QTc unmeasurable and undeterminable, sinus arrhythmia, sinus rhythm, and normal T wave morphology. An ECG at the Pre-Baseline visit (b) (6) was considered abnormal with sinus rhythm, sinus arrhythmia, and normal T wave morphology. An ECG at the Week 4 visit (b) (6) was normal. These ECGs were reviewed by the sponsor's cardiac electrophysiologist (CE) who interpreted them to be within normal limits. At the Early Termination visit (b) (6) the subject's blood pressure was 131/85 mmHg with a heart rate of 85 beats per minute; at the Week 2 Follow-up visit (b) (6) blood pressure was 135/90 mmHg with a heart rate of 111 beats per minute. An ECG at the Early Termination visit was normal. An ECG at the Week 2 Follow-up visit was considered abnormal with artifact, right axis deviation, sinus tachycardia, and normal T wave morphology. This ECG was also reviewed by the CE who interpreted it as a noisy tracing but otherwise within normal limits.

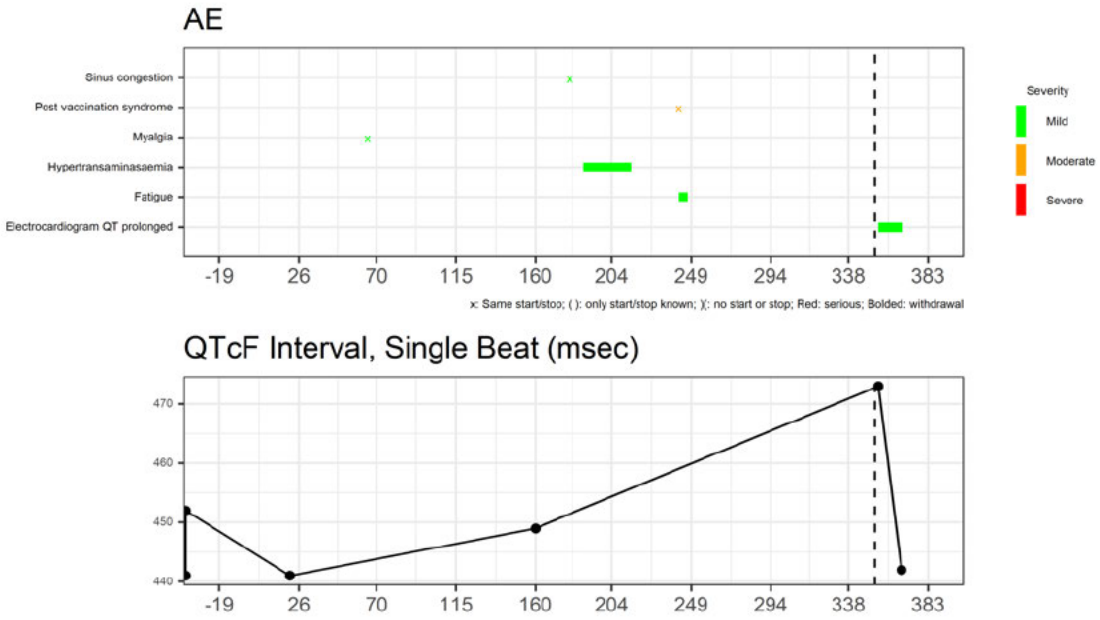
Figure 8. Narrative for Subject BHV3500-202-(b) (6)



Reviewer's Comment: The syncope event occurred at the same time as the severe migraine and no QTcF prolongation was observed.

- Subject BHV3500-202-(b) (6) (ECG QT prolonged): No narrative was provided by the sponsor for this subject. Figure 9 showed a timeline of AEs and QTcF. On (b) (6) (Study Day 355), the 35-year-old white female experienced a mild AE of ECG QT prolonged with QTcF observed at 473 msec. The event was resolved on (b) (6) (Study Day 369) with QTcF observed at 442 msec on the day before ((b) (6) Study Day 368). The subject's last exposure to zavegepant was on (b) (6) (Study Day 353), two days before the AE. The investigator considered this event possibly related to the study drug.

Figure 9. Narrative for Subject BHV3500-202-(b) (6)



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/

GIRISH K BENDE
08/03/2022 10:50:59 AM
Primary Reviewer: Anantha Ram Nookala, Ph.D.

ANANTHA RAM NOOKALA
08/03/2022 11:01:32 AM

JING SUN
08/03/2022 11:06:04 AM

DALONG HUANG
08/03/2022 11:56:02 AM

DONGLIN GUO
08/03/2022 12:58:18 PM

MICHAEL Y LI
08/03/2022 01:05:53 PM

YANYAN JI
08/03/2022 01:08:11 PM

CHRISTINE E GARNETT
08/03/2022 01:35:24 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	July 27, 2022
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 216386
Product Name and Strength:	Zavzpret (zavegepant) nasal spray, 10 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Biohaven Pharmaceutical Holding Company, Ltd.
FDA Received Date:	March 9, 2022
OSE RCM #:	2022-501
DMEPA 2 Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA 2 (Acting) Team Leader:	Stephanie DeGraw, PharmD

1 REASON FOR REVIEW

As part of the approval process for Zavzpret (zavegepant) nasal spray, the Division of Neurology 2 (DN 2) requested that we review the proposed Zavzpret prescribing information (PI), patient information (PPI), information for use (IFU), professional sample and trade container labels, blister labeling and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

On December 1, 2020, the Sponsor submitted a Type B meeting request - Chemistry, Manufacturing and Controls (CMC) to gain alignment on aspects of their migraine drug development program that included the adequacy of their human factors program strategy as it relates to development and eventual submission of human factors (HF) data in a future new drug application. DMEPA provided a written response in lieu of a meeting on February 12, 2021.[a] In the response, DMEPA informed the Sponsor to submit a use-related risk analysis (URRA), comparative analyses, and justification for not submitting the results of a HF validation study.

Thus, on August 20, 2021, the Applicant submitted a URRA and comparative analysis under IND 134120 to support their conclusion that an HF validation study was not needed to support the safe and effective use of their proposed zavegepant nasal spray.

The Applicant's URRA identified and evaluated the critical and non-critical tasks involved in the use of zavegepant nasal spray, the errors that users might commit, the tasks they may fail to perform, the potential negative consequences of use errors, and known use-related problems with similar products. Additionally, the comparative analysis provided for labeling comparison, a comparative task analysis and a physical comparison between their proposed product and a comparator (b) (4)

We reviewed the Applicant's URRA and comparative analysis for their proposed product and agree that the tasks evaluated appeared to be comprehensive and appropriate based on what the Applicant proposed for the design and intended use of this product. We also reviewed the URRA and comparative analysis to ensure that all potential use errors and risk involved in using the proposed product have been considered. Additionally, we did not identify any new or unique risks when compared to similar marketed nasal sprays. Therefore, based on our review of their URRA and comparative analyses under IND 134120 in OSE # 2021-1790[b], dated April 20, 2022, we concluded that a human factors (HF) validation study is not required to be submitted for Agency review in support of zavegepant nasal spray at this time.

---

[a] Killen, M. Type B Final Written Response for IND 134120, zavegepant. Silver Spring (MD): FDA, CDER, OSE (US); 2021 Feb.12.

[b] Adeolu, A. Use Related Risk Analysis Review for zavegepant. IND 134120. Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2020 OCT 13. RCM No.: 2021-1790.

2 MATERIALS 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
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

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 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), patient information (PPI), information for use (IFU), and the professional sample and trade container labels, blister labeling and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 (Table 2) for the Division and in Section 5 (Table 3) for Biohaven Pharmaceutical Holding Company, Ltd..

4 RECOMMEDATIONS FOR DIVISION OF NEUROLOGY 2 (DN 2)

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information (PI), Patient Information (PPI) and Instructions for Use (IFU): General Issues			
1.	The placeholder, TRADENAME is used throughout the PI, PPI and IFU labeling.	The proposed proprietary name, Zavzpret was found acceptable on May 4, 2022.[c]	The placeholder, TRADENAME, should be replaced with the conditionally acceptable name, Zavzpret, throughout the PI, PPI and IFU labeling.

[c] Mena-Grillasca, C. Proprietary Name Review for Zavzpret (NDA 216386). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 MAY 4. PNR ID No. 2022-1044724485

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 17 Patient Counseling			
1.	We note that similar products (e.g., (b) (4) (b) (4)) include additional instructions and warnings in Section 17 as compared to what is currently presented for Zavzpret.	Incomplete instructions and warnings may lead to improper use of the device and dosing errors.	We recommend adding the following statements after the first sentence in this section: Provide patients instruction on the proper use of ZAVAPRET nasal spray. Caution patients to avoid spraying the contents of the device in their eyes.
Information for Use (IFU)			
1.	The statement of strength and dosage form lacks sufficient prominence and is difficult to read.	The strength and dosage form are critical information that should appear prominently. We are concern that users may have difficulty identifying and reading the statement of strength and dosage form.	To increase readability, we recommend increasing the prominence/size of the expression of strength "10 mg" and dosage form "nasal spray." If more space is needed for this important information, consider decreasing the size of the logo to increase the white space and improve readability.

5 RECOMMENDATIONS FOR BIOHAVEN PHARMACEUTICAL HOLDING COMPANY, LTD.

Table 3. Identified Issues and Recommendations for Biohaven Pharmaceutical Holding Company, Ltd. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels, Blister Labeling (foil backing) and Carton Labeling (Trade and Professional Sample)			
1.	The proposed format for the expiration date (that is, MM YYYY) does not specify whether the month (that is, MM) will be displayed using numerical (for example, 06), or alphabetical (for example, JU) characters.	We are concerned that the current presentation of the expiration date may cause confusion. For example, presentation of the month as 'MM' does not clearly communicate whether 'MA' or 'JU' is for the months of March or May and the months of June or July, respectively. Therefore, we are unable to assess the expiration date format from a medication safety perspective, which may increase the risk for deteriorated drug medication errors.	Provide more information regarding the expiration format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. 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
2.	The statement of strength and dosage form lacks sufficient prominence and is difficult to read.	The strength and dosage form are critical information that should appear prominently. We are concern that users may have difficulty identifying and reading the statement	To increase readability, we recommend increasing the prominence/size of the expression of strength "10 mg" and dosage form "nasal spray." If more space is needed for this important information, consider decreasing the size of

Table 3. Identified Issues and Recommendations for Biohaven Pharmaceutical Holding Company, Ltd. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		of strength and dosage form.	the logo to increase the white space and improve readability.
3.	The important statement "Do not test spray, prime or press the plunger before use lacks prominence.	If users overlook this statement, there is risk of unintentional activation of the device which could result in dose omission or underdose when the patient attempts to administer the product.	We recommend increasing the prominence of the statement "Do not test spray, prime or press the plunger before use" by bolding the entire statement and/or increasing the font size as space allows.
Blister Labeling (foil backing) and Carton Labeling (Trade and Professional Sample)			
1.	As currently proposed, the "Recommended dosage: See prescribing information" statement includes the statement (b) (4)	Per the proposed prescribing information (PI), the recommended dosage in cases of moderate hepatic impairment or in patients on concomitant administration with OATP1B3 and NTCP inhibitors is "avoid another dose of Zavzpret nasal spray within 48 hours." Therefore, in these instances, the statement "only 1 dose per day" on the blister and carton labeling is not accurate. Inconsistent dosage recommendations may cause confusion and potentially lead to dosing errors.	Thus, we recommend removing the statement (b) (6) (b) (6) from the blister and carton labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Error! Reference source not found. presents relevant product information for Zavzpret that Biohaven Pharmaceutical Holding Company, Ltd. submitted on March 9, 2022, and the comparator product (b) (4)

Table 4. Relevant Product Information for Zavzpret (NDA 216386) and the Comparator Product (b) (4)		(b) (4)
Initial Approval Date	N/A	
Active Ingredient	Zavegepant	
Indication	Acute treatment of migraine with or without aura in adults	
Route of Administration	intranasal	
Dosage Form	nasal spray	
Strength	10 mg	
Dose and Frequency	10 mg given as a single spray in one nostril. Maximum dose in a 24-hour period is 10 mg. The safety of treating more than 8 migraines in a 30-day period has not been established.	
How Supplied	(b) (6)	
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]. Do not freeze. Do not test spray, prime, or press the plunger before use.	
Container Closure	Primary: Unit-dose, clear, USP (b) (6) glass vial with a grey (b) (6) stopper, (b) (6) Secondary: nasal spray device	

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 5, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, zavegepant and IND 134120. Our search identified one previous URRA and comparison analysis review[d], and we confirmed that a human factors (HF) validation study is not required to be submitted for Agency review in support of zavegepant nasal spray.

[d] Adeolu, A. Use Related Risk Analysis Review for zavegepant. IND 134120. Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2020 OCT 13. RCM No.: 2021-1790.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

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

- Commercial Presentation
  - Container label (device label)
  - Blister labeling (foil backing)
  - Carton labeling (6 count)
- Professional Sample Presentation
  - Container label (device label)
  - Blister labeling (foil backing)
  - Carton labeling (1 count)
- Instructions for Use (Image not shown) available from \\CDSESUB1\evsprod\nda216386\0001\m1\us\zav-ifu-proposed-in.pdf
- Patient Information (Image not shown) available from \\CDSESUB1\evsprod\nda216386\0001\m1\us\in-ppi.pdf
- Prescribing Information (Image not shown) available from \\CDSESUB1\evsprod\nda216386\0001\m1\us\in-draft-label-text.pdf

We also considered the Applicant's comparator product, Tosymra nasal spray [for comparison purposes only]. Labeling for comparator product, Tosymra nasal spray available from https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7260d567-3824-230d-836d-8065302baaec

F.2 Label and Labeling Images

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

---

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/

BEVERLY WEITZMAN
07/27/2022 02:35:43 PM

STEPHANIE L DEGRAW
07/27/2022 04:22:45 PM