CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216951Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Integrated Review

NDA Number	216386
Link to EDR	\\CDSESUB1\evsprod\NDA216386
Submission Date	09-Mar-2022
Submission Type	505(b)(1) Application (Standard Review)
Brand Name	ZAVZPRET
Generic Name	Zavegepant Hydrochloride ('BHV-3500')
Dosage Form (Strength)	Nasal Spray (10 mg)
Proposed Indication	Acute treatment of migraine with or without aura in adults
Applicant	Biohaven Pharmaceuticals, Inc.
Associated IND	134120
OCP Review Team	Suresh Babu Naraharisetti, Ph.D., Liu, Jie Ph.D., Atul Bhattaram, Ph.D., Yuching Yang, Ph.D., Gopichand Gottipati, Ph.D. Sreedharan Sabarinath, Ph.D., Ramana Uppoor, Ph.D.
OCP Final Signatory	Mehul Mehta, Ph.D.

Table of Contents

List of Abbreviations

AE	Adverse event
AUC	Area under the concentration-time curve
$AUC_{0\text{-}inf}$	AUC from time 0 to extrapolated to infinity
BCRP	Breast cancer resistance protein
BSEP	Bile salt export pump
CGRP	Calcitonin gene-related peptide receptor
C_{max}	Maximum (peak) drug concentration
CYP	Cytochrome P-450 enzyme
DDI	Drug-Drug Interaction
MATE	Multidrug and toxin extrusion transporter
MBS	Most bothersome symptom
MRPs	Multidrug resistance associated proteins
NDA	New Drug Application
NTCP	Sodium taurocholate co-transporting polypeptide
OAT	Organic anion transporter
OATP	Organic anion-transporting polypeptide
OCT	Organic cation transporter
PBPK	Physiologically based pharmacokinetic model
PD	Pharmacodynamics
P-gp	P-glycoprotein
PK	Pharmacokinetics
T_{max}	Time of maximum (peak) drug concentration
UDS	Unit Dose System

1. Executive Summary

In this original New Drug Application (NDA), Biohaven Pharmaceuticals Inc. is seeking approval of Zavegepant intranasal (IN) spray (NDA 216386) for the acute treatment of migraine in adults. Zavegepant (also referred as 'BHV-3500') is a new molecular entity (NME) and is not marketed in the US for any indication. It is a calcitonin gene-related peptide (CGRP) receptor antagonist developed for IN administration. Recently, several therapies targeting CGRP pathway such as Erenumab (BLA-761077, 5/17/2018), Fremanezumab (BLA-761089, 9/14/2018), Galcanezumab (BLA-761083, 9/27/2018), Eptinezumab (BLA-761119, 2/21/2020), and Atogepant (NDA 215206, 09/28/2021) have been approved by the FDA for migraine prevention in adults. Ubrogepant (NDA-211765, 12/23/2019) was approved for the acute treatment of migraine in adults, while Rimegepant (NDA-212728, 2/27/2020 & 4/11/2022) was approved for both acute treatment of migraine and episodic migraine prevention.

The applicant is relying on 2 randomized, double-blind, single-dose, placebo-controlled efficacy studies (BHV3500-201 and BHV3500-301), and one open-label long-term safety study (BHV3500-202) in patients with acute migraine. The patients with acute migraine were defined as those who had at least 1 year history of migraine (with or without aura) and not more than 8 attacks of moderate or severe pain intensity per month within last 3 months (International Classification of Headache Disorders criteria; 3rd Ed. beta, 2013).

Study BHV3500-201 evaluated single dose of 5, 10 and 20 mg IN zavegepant. Only the 10 and 20 mg arms met the prespecified criteria for co-primary efficacy endpoints: pain freedom and absence of the most bothersome migraine-associated symptom (MBS) at 2 hours, while patients in 20 mg arm did not show meaningful improvements in efficacy compared to those in 10 mg arm. Study BHV3500-301 evaluated single dose of 10 mg IN zavegepant and met the prespecified criteria for co-primary efficacy endpoints noted above. Study BHV3500-202 evaluated and demonstrated the long-term safety of only the 10 mg dose-level. The applicant is seeking approval for 10 mg zavegepant given as a nasal spray in one nostril, and the maximum allowed dose in 24-hours is 10 mg. In addition to the efficacy/safety studies, the applicant included 11 Phase 1 studies.

The primary focus of this review is to evaluate the appropriateness of dose adjustments based on intrinsic and extrinsic factors.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) team has reviewed the information submitted under this NDA and recommends approval of 10 mg IN dose of zavegepant (with the maximum dose of 10 mg in a 24-hour period) for the acute treatment of migraine with or without aura in adults. The key review issues with specific recommendations and comments are summarized below in Table 1-1:

Table 1-1 Summary of Review Issues and OCP Recommendations

Review Issues	Recommendations and Comments
Evidence of effectiveness:	The evidence of effectiveness of 10 mg IN zavegepant for acute treatment of migraine in adults is from two, multi-center, double-blind, placebo-controlled, single-dose studies, BHV3500-201 and BHV3500-301.
General dosing instructions:	The recommended dose is 10 mg given as a single spray in one nostril. The maximum dose in a 24-hour period is 10 mg.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• **Severe hepatic impairment (Child-Pugh C):** Zavegepant has not been studied in patients with severe hepatic impairment (Child-Pugh C). Avoid use of zavegepant in patients with severe hepatic impairment. • **Severe renal impairment (CLcr 15-29 mL/min)**: In patients with severe renal impairment, accumulation of uremic solutes has been reported to inhibit OATP transporter, which can increase zavegepant exposures. Avoid use of zavegepant in patients with severe renal impairment. • **Subjects with kidney failure (CLcr < 15 mL/min)**: Zavegepant has not been studied in patients with kidney failure or in patients on dialysis. Avoid use of zavegepant in patients with kidney failure. • **Inhibitors of OATP1B3 or NTCP transporters**: Zavegepant is a substrate for OATP1B3 and NTCP transporters. Increased plasma concentrations of zavegepant were observed when concomitantly administered with steady-state rifampin (OATP1B3 and NTCP inhibitor). Avoid concomitant use of zavegepant with the drugs that inhibit OATP1B3 or NTCP. • **Inducers of OATP1B3 or NTCP transporters:** Zavegepant is a substrate for OATP1B3 and NTCP transporters. Concomitant administration of zavegepant with inducers of OATP1B3 or NTCP transporters may result in reduced plasma concentrations of zavegepant. Avoid concomitant use of zavegepant with the drugs that induce OATP1B3 or NTCP.

Review Issues	Recommendations and Comments
Dosing in patient subgroups (intrinsic and extrinsic factors)	• **Intranasal decongestants:** Concomitant administration of zavegepant with intranasal decongestants may decrease the absorption of zavegepant. Avoid concomitant administration of intranasal decongestants with zavegepant. When concomitant use is unavoidable, intranasal decongestants should be administered at least 1 hour after zavegepant administration.
Bridge between the "to-be-marketed" and clinical trial formulations	The zavegepant nasal spray is a solution of 10 mg zavegepant free base (equivalent to (b) (4) mg of zavegepant hydrochloride) in a buffered aqueous solution ((b) (4) mg/mL). The composition of the formulation and the design of the device used in the pivotal trials and commercial use (to-be-marketed) are the same. Therefore, no PK bridging studies are required.

1.2 Post-Marketing Requirement and Commitment

None

2. Summary of Clinical Pharmacology Assessment

2.1 The Pharmacology and Clinical Pharmacokinetics

Mechanism of Action:

Zavegepant is a CGRP receptor antagonist developed for IN administration. CGRP is an endogenous 37 amino acid peptide contained within pain signaling nociceptive afferents. Zavegepant reportedly binds to the human CGRP receptor and antagonizes CGRP receptor function, thus inhibiting CGRP-induced enhancement of pain signaling, blocking CGRP-induced vasodilation, and halting CGRP-induced neurogenic inflammation.

Absorption:

The median Tmax of zavegepant with 10 mg nasal spray was 0.54 h. The absolute bioavailability of zavegepant, determined using population pharmacokinetics (PPK) approach after 10 mg intranasal dose was ~5%. Following once daily IN zavegepant dosing of 10 mg and 20 mg for 14 days, and 40 mg (2 x 20 mg administered with a 2-hour gap between the 2 doses) for 8 days, there was minimal accumulation (up to 18%). Zavegepant exhibits slightly less than dose-proportional increase in the exposure following single IN dose administration over the dose range from 1 mg to 40 mg.

Distribution:

The mean apparent volume of distribution of intranasal zavegepant is approximately 1774 L. Zavegepant is approximately 90% bound to human plasma proteins.

Elimination:

Metabolism

Based on in vitro studies, zavegepant is primarily metabolized by CYP3A4. After a single IV dose of 5 mg [^{14}C]-zavegepant, unchanged zavegepant was the most prevalent circulating component in the human plasma (~ 90%). No major metabolites (i.e., > 10%) of zavegepant were detected in plasma.

Excretion

The effective elimination half-life in healthy subjects following a single dose of 10 mg zavegepant nasal spray was approximately 6.6 hours. The mean apparent clearance of intranasal zavegepant was 266 L/h. Fecal excretion (biliary elimination) plays a major role while renal plays a minor role in the elimination for zavegepant: 80% and 11% of the dose was recovered as unchanged zavegepant in feces and urine, respectively.

Specific Populations:

Hepatic Impairment

In a clinical study comparing PK of zavegepant in subjects with moderate hepatic impairment (Child-Pugh B) compared to that in subjects with normal hepatic function, zavegepant $AUC_{0\text{-}inf}$ was 1.9-fold higher and Cmax was 16% higher in subjects with moderate hepatic impairment (Child-Pugh B). Based on minimal accumulation (given the short effective half-life and once daily dosing interval) and tolerable safety profile noted in a multiple ascending dose study, upon discussion with clinical division, the review team recommends that no dose adjustment is needed in patients with moderate hepatic impairment. Since the magnitude of the impact of mild impairment on PK is expected to be lower than that observed with moderate hepatic impairment, no dose adjustment is needed in mild hepatic impairment (Child Pugh A).

The impact of severe hepatic impairment has not been studied. Therefore, it is recommended to avoid use of zavegepant in patients with severe hepatic impairment (Child-Pugh C) (see Section 3.3.2).

Renal Impairment

The mass balance study showed that the renal route plays a minor role in the clearance of zavegepant (11% of dose recovered as unchanged zavegepant in urine). The effect of renal impairment on zavegepant PK has not been studied in a dedicated renal impairment study. PPK analysis indicated that there is no clinically significant effect on the PK of zavegepant in subjects with estimated creatinine clearance (CLcr) ranging from 52 to > 90 mL/min. In-vitro and in-vivo studies indicate that zavegepant is a substrate for OATP1B3 transporter. It has been reported in the literature that uremic solutes can accumulate in subjects with severe renal impairment (CLcr < 30 mL/min). Accumulation of uremic solutes has been reported to inhibit OATP transporters[1], that can result in increased zavegepant exposures. Therefore, it is recommended to avoid use of zavegepant in patients with severe renal impairment (CLcr 15 – 29 mL/min). The impact of kidney failure or dialysis on the PK of zavegepant was not evaluated. Therefore, it is recommended to avoid use in patients with kidney failure (CLcr < 15 mL/min).

Effects of Body Weight, Gender, Race, Ethnicity and Age

Body weight, gender, race, ethnicity and age did not have a clinically relevant effect on the PK of zavegepant. Please refer to Section 4.2 for additional details.

[1] Ming-Liang Tan et al; Effect of Chronic Kidney Disease on Nonrenal Elimination Pathways: A Systematic Assessment of CYP1A2, CYP2C8, CYP2C9, CYP2C19, and OATP; PMID: 28990182

2.2. Dosing and Therapeutic Individualization

2.2.1 General dosing

For the acute treatment of migraine, the recommended dose is 10 mg given as a single spray in one nostril. The maximum dose in a 24-hour period is 10 mg.

2.2.2 Therapeutic individualization

Drug Interactions

Inhibitors of CYP3A4 and P-gp:

In a dedicated drug interaction study, concomitant administration of a single dose of 10 mg zavegepant IN with itraconazole (200 mg once daily; at steady state), a strong CYP3A4 and P-gp inhibitor did not result in a clinically relevant effect on the exposures of zavegepant. Therefore, no dosage adjustment for zavegepant is recommended when concomitantly administered with inhibitors of CYP3A4 and P-gp.

Since the impact on the zavegepant exposures with a moderate or a weak inhibitor will be lower than that with strong inhibitors, no dosage adjustment for zavegepant is recommended when concomitantly administered with moderate or weak inhibitors of CYP3A4 and P-gp.

Inducers of CYP3A4 and P-gp:

Considering the low metabolic clearance of zavegepant and the lack of a significant effect with a strong CYP3A4 inhibitor on the PK of IN zavegepant, drug interactions with CYP3A4 and P-gp inducers is not expected to have a clinically significant effect on zavegepant exposures. Therefore, no dose adjustment of zavegepant is recommended when concomitantly administered with inducers of CYP3A4 and P-gp.

Inhibitors of OATP1B3 or NTCP:

Zavegepant is a substrate for OATP1B3 and NTCP transporters. Concomitant administration of single dose of 100 mg zavegepant oral capsule with rifampin (600 mg once daily; at steady state), a strong inducer of P-gp and CYP3A, and an inhibitor of OATP1B3 and NTCP, showed 2.3-fold and 2.2-fold increase in zavegepant AUC and Cmax, respectively. This observed effect is a composite of the induction effect on P-gp and CYP3A and the inhibition effect on OATP1B3 and NTCP transporters, and therefore, likely is an underestimate of the OATP1B3 or NTCP-mediated inhibition effect. The review team recommends avoiding the concomitant use of zavegepant with inhibitors of OATP1B3 or NTCP.

Inducers of OATP1B3 or NTCP

The applicant did not conduct a dedicated study to evaluate the impact of OATP1B3 or NTCP inducers on PK of zavegepant. Concomitant administration of zavegepant with

inducer of OATP1B3 or NTCP transporters may result in reduced plasma concentrations of zavegepant. The review team recommends avoiding the concomitant use of zavegepant with the drugs that induce OATP1B3 or NTCP.

Sumatriptan:

Sumatriptan is indicated for the acute treatment of migraine attacks. In a dedicated PK-PD DDI study, the co-administration of sumatriptan (12 mg, given as two 6 mg subcutaneous doses separated by one hour) with 20 mg IN zavegepant did not result in a clinically significant change in the PK of sumatriptan or zavegepant, or cause elevations in mean arterial BP or systolic or diastolic BP. Therefore, co-administration of zavegepant with sumatriptan can be allowed without dosage modification.

Oral Contraceptives:

In a dedicated study, co-administration of oral contraceptive ethinyl estradiol-levonorgestrel, EE-LNG (0.02 mg- 0.1 mg) with 20 mg IN zavegepant did not result in a clinically significant change in the PK of EE or LNG. Therefore, oral contraceptives may be co-administered with IN zavegepant without dosage modification.

Specific Populations

Hepatic Impairment

In a dedicated clinical study comparing PK of zavegepant in subjects with moderate hepatic impairment (Child-Pugh B) compared to subjects with normal hepatic function, higher exposures of zavegepant ($AUC_{0\text{-}inf}$ by 1.9-fold and Cmax by 16%) were observed in moderate hepatic impairment. Based on the observed increase in exposure of zavegepant, the applicant recommended (b) (4) (b) (4) in patients with moderate hepatic impairment. Based on minimal accumulation (given the short effective half-life and once daily dosing interval) and tolerable safety profile noted in multiple ascending dose study, upon discussion with clinical division, the review team recommends that no dose adjustment is needed in patients with moderate hepatic impairment. Since the magnitude of the impact of mild impairment on PK is expected to be lower than that observed with moderate hepatic impairment, no dose adjustment is needed in mild hepatic impairment (Child Pugh A).

The impact of severe hepatic impairment on the PK of zavegepant has not been studied. It is recommended to avoid zavegepant in patients with severe hepatic impairment (see Section 3.3.3).

Renal Impairment

The effect of renal impairment has not been studied in a dedicated renal impairment study. The mass balance study showed that the renal route plays a minor role in the

clearance of zavegepant (11% of dose recovered as unchanged zavegepant in urine). The PPK analysis indicated that there is no clinically significant effect on the PK of zavegepant in subjects in patients with estimated Clcr ranged from 52 to >90 mL/min. In-vitro and in-vivo studies indicate that zavegepant is a substrate for OATP1B3 transporter. It has been reported in the literature that uremic solutes can accumulate in subjects with severe renal impairment (CLcr < 30 mL/min). Accumulation of uremic solutes has been reported to inhibit OATP transporters, resulting in increased zavegepant exposures. Therefore, it is recommended to avoid use of zavegepant in patients with severe renal impairment (CLcr 15 – 29 mL/min). The impact of kidney failure or dialysis on PK of zavegepant was not evaluated. Therefore, it is recommended to avoid use in patients with kidney failure (CLcr < 15 mL/min) (see Section 3.3.3).

Other Specific Populations:

Based on the population PK analysis, body weight, gender, race, ethnicity, and age did not have a clinically relevant effect on the PK of zavegepant. Refer to Section 4. for additional details.

2.2.3 Outstanding Issues

None.

2.2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology has the following labeling concepts to be included in the final package insert.

- The recommended dose is 10 mg given as a single spray in one nostril. The maximum dose in a 24-hour period is 10 mg.
- No dose adjustment is necessary in mild and moderate renal impairment, CLcr >30 mL/min (see Section 3.3.3). Accumulation of uremic solutes in subjects with severe renal impairment can affect OATP activity, potentially resulting in increased zavegepant (an OATP1B3 substrate) exposures in such subjects. Therefore, it is recommended to avoid use of zavegepant in patients with severe renal impairment (CLcr 15 – 29 mL/min). The impact of kidney failure or dialysis on PK of zavegepant was not evaluated. Therefore, it recommended to avoid use in patients with kidney failure (CLcr < 15 mL/min) (see Section 3.3.3).
- No dose adjustment is required in subjects with mild hepatic impairment (Child-Pugh A). In patients with moderate hepatic impairment (Child-Pugh B), zavegepant exposures, $AUC_{0\text{-}inf}$ increased by 1.9-fold and Cmax by 16% relative to matched healthy controls. Based on minimal accumulation and tolerable safety profile noted

after QD administration for 14 days of 20 mg IN zavegepant in MAD study, no dose adjustment is necessary in patients with moderate hepatic impairment. Zavegepant has not been studied in patients with patients with severe hepatic impairment (Child-Pugh C). It is recommended to avoid use of zavegepant in patients with severe hepatic impairment (see Section 3.3.3).

- No dose adjustment is necessary based on body weight, age, gender, race, and ethnicity (see Section 3.3.3).
- Concomitant administration of IN zavegepant with a strong inhibitor of CYP3A4 and P-gp (itraconazole) did not result in a clinically significant change in zavegepant exposures. No dose adjustment of zavegepant is necessary with inhibitors of CYP3A4 /P-gp (see Section 3.3.4).
- Considering the low metabolic clearance and the lack of a significant effect with a strong CYP3A4 inhibitor on the PK of IN zavegepant, drug interactions with CYP3A4 and P-gp inducers is not expected to have a clinically significant effect on zavegepant exposures. Therefore, no dose adjustment of zavegepant is necessary with inducers of CYP3A4 and P-gp.
- Concomitant oral administration of 100 mg oral zavegepant with rifampin at steady state (strong CYP3A and P-gp inducer, and OATP1B3 and NTCP inhibitor) resulted in 2.3-fold increase in AUC and 2.2-fold in Cmax of zavegepant. This effect is a composite of induction of CYP3A and P-gp, and inhibition of OATP1B3 and NTCP. Therefore, the magnitude of OATP1B3 and NTCP-mediated interaction is likely to be an underestimate. Therefore, it is recommended to avoid concomitant use of zavegepant with the drugs that inhibit OATP1B3 or NTCP (see Section 3.3.4).
- Concomitant administration of zavegepant with inducers of OATP1B3 or NTCP transporters may result in reduced plasma concentrations of zavegepant. It is recommended to avoid the concomitant use of zavegepant with the drugs that induce OATP1B3 or NTCP (see Section 3.3.4).
- Concomitant administration of zavegepant with intranasal decongestants may decrease the absorption of zavegepant. It is recommended to avoid concomitant administration of intranasal decongestants with zavegepant. When concomitant use is unavoidable, intranasal decongestants should be administered at least 1 hour after zavegepant administration (see Section 3.3.4).
- No clinically significant PK interactions were observed with oral contraceptives (see Section 3.3.4).

- No clinically significant pharmacokinetic or pharmacodynamic (changes in resting blood pressure) interaction was observed between sumatriptan and zavegepant (see Section 3.3.4).

3. Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

Zavegepant is a human CGRP receptor antagonist, formulated for IN spray administration, comprised of BHV-3500 (free base) at (b) (4) mg/mL in a solution containing (b) (4) and dextrose at pH 6.0. The product is delivered using a single-dose nasal device (b) (4)

The clinical development program to demonstrate the safety and efficacy for Zavegepant consisted of 11 phase-1 clinical studies, two efficacy studies (Study BHV3500-201 and BHV3500-301) and one long-term safety study (BHV3500-202).

3.2 General Pharmacological and Pharmacokinetic Characteristics

Table 3-1 Summary of Pharmacological and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Zavegepant is a human calcitonin gene-related peptide receptor antagonist.
QTc Prolongation	At doses up to 4 times the recommended daily dose (10 mg), zavegepant does not prolong the QT interval to any clinically relevant extent. (Refer to the QT-IRT review in DAARTS dated 08/03/2022).
General Information	
Bioanalysis	Zavegepant plasma concentrations were determined using a validated LC-MS/MS method (see Section 4.1).
Migraine vs. non-migraine periods	No clinically significant difference in zavegepant exposures were observed during a migraine attack vs. non-migraine attack period.
Dose Proportionality	Zavegepant exhibits slightly less than dose-proportional increase in the exposure following single IN dose administration over the dose range from 1 mg to 40 mg.
Accumulation	Zavegepant is intended for maximum single dose of 10 mg intranasal dose in a 24-h period. No significant accumulation was observed following repeated once daily dosing for 14 days.

Pharmacokinetic Variability	Coefficient of variation for 10 mg IN dose after 14 daily doses was ~51% and 47% for AUCtau and Cmax, respectively.
Absorption	
Bioavailability	Absolute bioavailability of zavegepant determined using PPK approach after 10 mg intranasal dose was ~5%.
Tmax	Median Tmax of zavegepant with 10 mg nasal spray was 0.54 h.
Distribution	
Apparent volume of distribution	1774 L.
Protein Binding	~90%
Transporters	Zavegepant is a substrate for P-gp, MATE1, MATE2-K, OATP1B3 and NTCP, but not a substrate of BSEP, BCRP, OATP1B1, OAT1, OAT3, OCT2, BSEP, MRP2, MRP3, or MRP4. Zavegepant is not an inhibitor of P-gp, BCRP, OAT1/3, OATP1B1/1B3, OCT2, MATE1,2-K at clinically relevant concentrations.
Elimination	
Mean effective elimination half-life	~ 6.5 hours
Metabolic Pathway	Zavegepant is primarily metabolized by CYP3A4, in-vitro. The results from mass-balance study showed that the hepatic metabolism of zavegepant was low and did not show major circulating metabolites. Following a single intravenous dose of 5 mg [14C]-zavegepant to healthy males, unchanged zavegepant was the most prevalent (~90%) circulating component in plasma.
Inhibitor / Inducer	In-vitro studies showed that zavegepant is not an inhibitor of CYP1A2, 2C9, 2C19, 2B6, 2D6 and 3A4. It is not a time-dependent inhibitor of CYP2C9, 2C19, 2D6, 2B6, 2C8, and 3A4. In-vitro studies indicated that zavegepant showed little to no induction of CYP1A2, 2B6, or 3A4/5.
Excretion Pathway	Fecal excretion is the main route of elimination of unchanged zavegepant (80%) and, renal route was a minor pathway (11%) in excretion of zavegepant based on the mass-balance study.

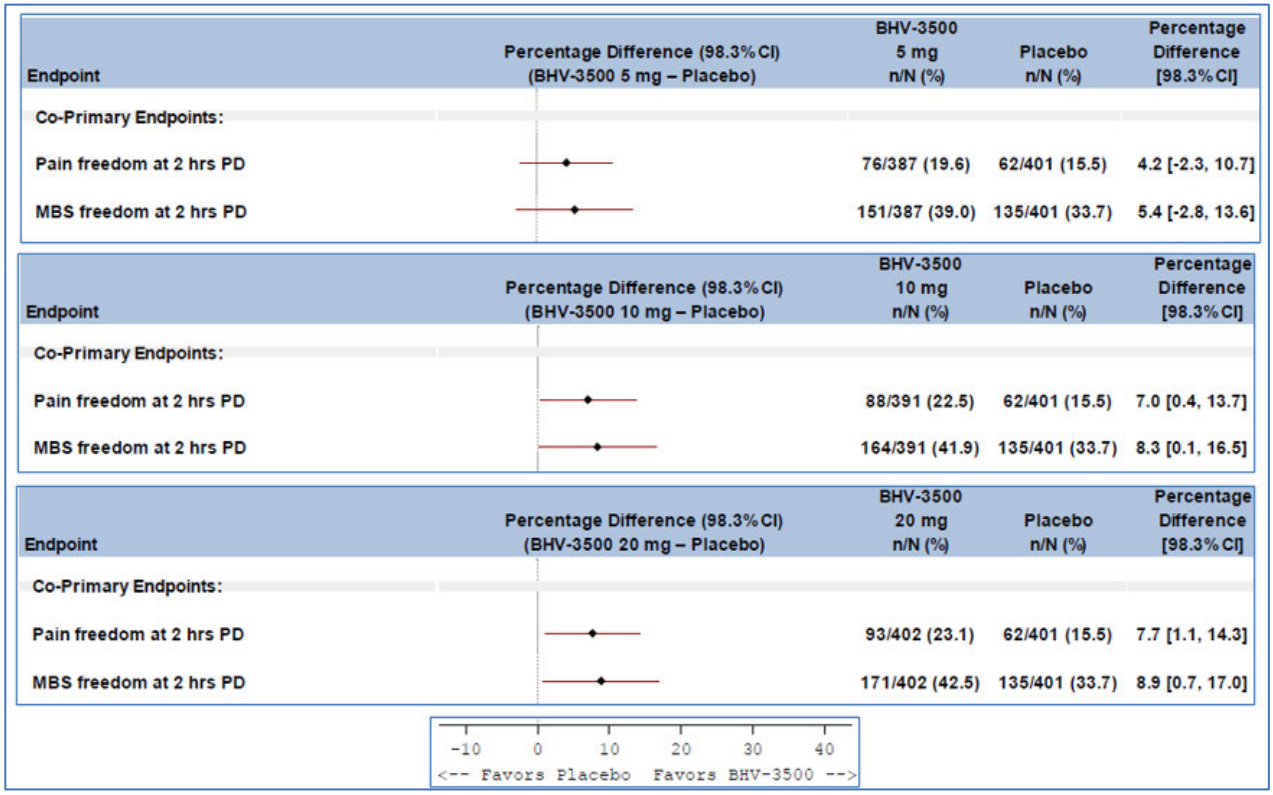
3.3 Clinical Pharmacology Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The primary evidence of effectiveness of zavegepant for the treatment of acute migraine is based on two randomized, double-blind, placebo-controlled single-attack trials BHV3500-201 and BHV3500-301. Study BHV3500-201 evaluated efficacy of 5, 10, and 20 mg administered as a single IN dose, while study BHV3500-301 evaluated efficacy of a single IN dose of 10 mg zavegepant. These trials enrolled male or female patients who were 18 years and older and had at least 1 year history of migraine attacks (with or without aura) consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd edition, with an age of onset prior to 50 years of age, migraine attack lasting 4 to 72 hours if untreated and not more than 8 attacks of moderate or severe intensity per month within the last 3 months (please refer to Clinical and Statistics reviews for additional details on exclusion and inclusion criteria). Both trials included a screening period (up to 28 days) and an acute treatment period of 45 days.

Study BHV3500-201 met the prespecified criteria for both co-primary efficacy endpoints: pain freedom and absence of the most bothersome migraine-associated symptom (MBS) [photophobia, phonophobia, or nausea] at 2 hours, following single doses of 10 mg and 20 mg, while 5 mg did not (results summarized in figure below). Additionally, patients in 20 mg arm did not show meaningful improvements in efficacy compared to those in 10 mg arm. Based on these results, 10 mg IN was selected for further evaluation.

Figure 3-1 Forest plot of primary endpoints, zavegepant 5 mg, 10 mg, and 20 mg versus placebo (Study BHV3500-201)

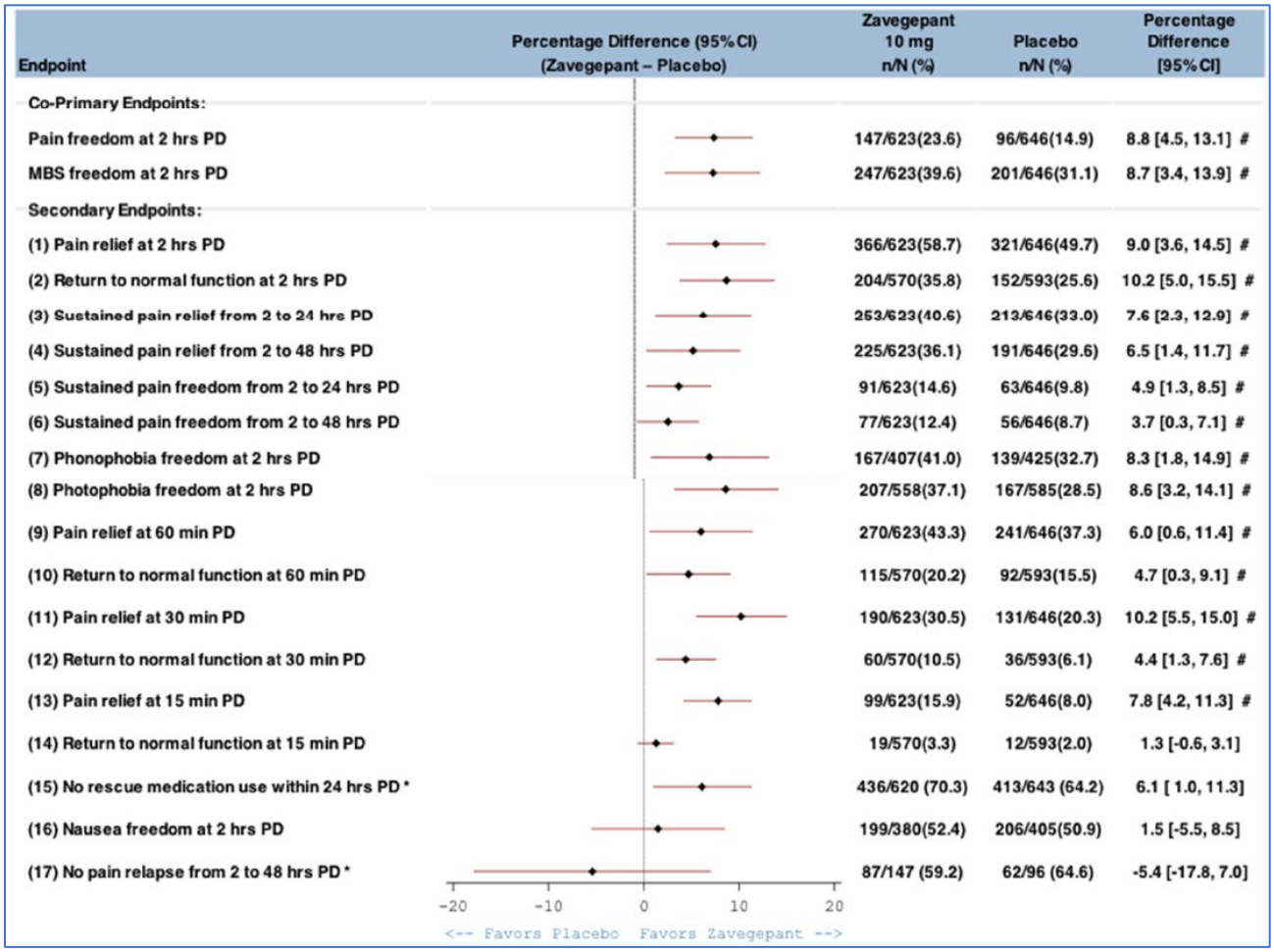


Source: Study BHV3500-201 clinical study report, Figures 10-1, 10-2 and 10-3 on pages 51, 53 and 55

Study BHV3500-301 met the prespecified criteria for 10 mg zavegepant for co-primary endpoints noted above. The results are summarized in figure below.

Please refer to statistical review Drs. Ye Li and John Lawrence for additional details on primary and secondary endpoint analyses.

Figure 3-2 Forest plot of co-primary and secondary endpoints (BHV3500-301)



Source: Study BHV3500-301 clinical study report, Figures 11-1, on pages 43 and 44

Study BHV3500-202 is a multicenter, open-label study to assess the safety and tolerability of long-term use of zavegepant 10 mg IN, taken up to 8 times per month (28 days), in 600 subjects with migraine. Overall, the study of zavegepant IN 10 mg demonstrates the favorable safety profile across a variety of safety endpoints, including AE assessments, clinical laboratory testing including LFTs, vital signs, and ECGs. The most frequently reported treatment-emergent AEs were dysgeusia, nasal discomfort, COVID-19, nausea, throat irritation, and nasal congestion. Please refer to the clinical review by Drs. Ryan Kau and Heather Fitter for additional details.

3.3.2 Is the proposed dosing regimen appropriate for the general population for which the indication is being sought?

Yes, studies BHV3500-201 and BHV3500-301 demonstrated that the 10 mg dose administered as IN spray is superior to placebo for the acute treatment of migraine for both pain freedom and absence of the most bothersome migraine-associated symptom at 2 hours (See Section 3.3.1). Even though the 20 mg was superior to placebo in one of the studies (BHV3500-201), the efficacy endpoints were comparable to 10 mg dose. The applicant intends to market only 10 mg dose strength and is seeking approval only for 10 mg dose. Study BHV3500-202 demonstrated long-term safety for the 10 mg dose.

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

Yes, zavegepant should be avoided in patients with severe renal impairment and kidney failure, and severe hepatic impairment. Population pharmacokinetic analysis did not reveal a clinically significant impact of body weight, gender, race, ethnicity and age on the exposures of zavegepant. Therefore, no dose adjustment is necessary based on these intrinsic factors.

Renal Impairment

The results from the mass-balance study indicate that renal route plays a minor role in the clearance of zavegepant. Following a single IV 5 mg [^{14}C]-zavegepant dose, only ~11% of the dose was recovered as unchanged zavegepant in the urine. The effect of renal impairment has not been studied through a dedicated renal impairment study. Based on PPK analysis, no clinically significant effect on the PK of zavegepant was observed in subjects with estimated creatinine clearance, CLcr in the range from 52 to > 90 mL/min.

The review team's recommendations and relevant considerations are summarized below for patients with CLcr <30 mL/min, who constitute patients with severe renal impairment (CLcr 15-29 mL/min) and kidney failure (CLcr < 15 mL/min):

<u>Severe Renal Impairment</u>

Zavegepant is a substrate for CYP3A, P-gp OATP1B3 and NTCP. The applicant conducted a DDI study with oral zavegepant and rifampin (OATP1B3 and NTCP inhibitor, and CYP3A and p-gp inducer) at steady state. However, the design of the available study makes it difficult to tease out the relative contribution of CYP3A and/or p-gp induction as well as OATP1B3 or NTCP-inhibition effects of rifampin on zavegepant exposure (see Section 3.3.4). Therefore, the observed 2.3-fold increase in zavegepant exposures with rifampin is likely an underestimation of the OATP1B3 and/or NTCP inhibition. Assuming a worst-case scenario of accumulation of uremic solutes (which is reported to occur in

patients with severe renal impairment) behaving like a “strong” inhibitor of OATP and/or NTCP, the exposures could be > 2.3-fold, as seen with the rifampin DDI study. This is the basis for review team’s recommendation to avoid zavegepant use in severe renal impairment.

Kidney failure

The impact of kidney failure or dialysis (CLcr < 15 mL/min) on PK of zavegepant was not studied. Zavegepant is 90% plasma protein bound. While the impact of dialysis has not been studied, during the dialysis, in addition to removal of uremic solutes, it is likely that the zavegepant could also be removed to a certain degree. Since the true impact of dialysis on the exposure of zavegepant cannot be reliably predicted, the review team recommends avoid use of zavegepant in patients with kidney failure.

Hepatic Impairment

The applicant conducted a study (Study # BHV3500-108), an open-label, parallel group study to evaluate the PK of 10 mg IN zavegepant in subjects with moderate hepatic impairment (Child Pugh B, n=8) compared to that in healthy matched controls (n=8). The results show that moderate hepatic impairment increased the exposure of zavegepant, approximately 1.9-fold in $AUC_{0\text{-inf}}$ and 16% in Cmax following a single dose of IN zavegepant 10 mg when compared to normal hepatic function (Table 3-2).

In both the treatment groups, unbound zavegepant concentrations were measured at 0.5- and 4-hours post-dose. The geometric mean Fu (fraction unbound) of zavegepant was similar in subjects with moderate hepatic impairment (0.13) and in subjects with normal hepatic function (0.11). The Fu was similar at 0.5- and 4-hours postdose for individual subjects regardless of hepatic function.

Table 3-2 Summary of total zavegepant PK parameters following a single dose of IN zavegepant 10 mg in subjects with moderate hepatic impairment or subjects with normal hepatic function [Study # BHV3500-108]

Group (N)	PK Parameters		Geometric Mean Ratio (90 % CI)	
	C_{max} (ng/mL)	$AUC_{0\text{-inf}}$ (h.ng/mL)	C_{max} (ng/mL)	$AUC_{0\text{-inf}}$ (h.ng/mL)
Normal hepatic function (N = 8)	20 (53%)	44 (51%)		
Moderate hepatic impairment (N = 8)	23 (67%)	84 (47%)[2]	1.16 (0.69 to 1.95)	1.93 (1.12 to 3.33)

[2]n = 7; PK parameters are presented as geometric mean (% CV); *Source:* Reviewer confirmed sponsor’s analysis.

Based on the observed 1.9-fold increase in AUC of zavegepant in patients with moderate hepatic impairment (HI), the applicant recommended (b) (4) (b) (4) The observed ~2-fold increase in AUC is equivalent to that following 20 mg IN dose, which showed comparable efficacy for primary and secondary efficacy endpoints at 10 mg IN in study 201. Although the long-term safety for 20 mg IN dose was not evaluated, the review team recommends that no adjustment in moderate HI is necessary based on the following considerations:

- The MAD study in health volunteers evaluated 10 mg, 20 mg QD dosing for 14 days and 40 mg (2 x 20 mg administered with a 2-hour gap between the 2 doses) QD dosing for 8 days. Based on discussion with Clinical, the observed adverse events with 20 mg QD dosing for 14 days were not particularly concerning (albeit the data is from a small number of patients). The MAD study results showed the effective half-life was 6.5 hours, and minimal accumulation with QD dosing (up to 18%). The proposed indication is acute treatment of migraine, and maximum allowed dose in a 24-hour period is a single dose. Therefore, the potential for significant accumulation with multiple dosing of 10 mg in subjects with moderate HI is unlikely.
- Zavegepant does not undergo significant hepatic metabolism, and 80% of the 5 mg [^{14}C]-zavegepant intravenous dose is excreted unchanged in feces. Further, no major metabolites have been identified in mass-balance study. The absolute bioavailability of IN zavegepant determined using PPK approach was reported to be ~5%.
- The safety profile for zavegepant was reasonably characterized in the clinical program and clinical team noted the AEs were not concerning. Further, the cumulative safety data generated for the recently approved therapies that target CGRP pathways did not show cardiovascular related AEs (which were initially thought to occur based on the mechanism of action targeting CGRP pathway).

For mild hepatic impairment patients, since the magnitude of the impact on PK is expected to be lower than that observed with moderate hepatic impairment, no dose adjustment is needed in mild hepatic impairment (Child Pugh A). The impact of severe hepatic impairment on the PK of zavegepant has not been studied. Therefore, the review team recommends to avoid use in patients with severe hepatic impairment (Child Pugh C).

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Zavegepant 10 mg IN spray is not expected to have food-effect, and therefore the applicant did not evaluate the impact of food-intake on PK. Avoid concomitant use of zavegepant with OATP1B3 or NTCP inhibitors or inducers, and intranasal decongestants.

Drug Interactions

Modulators of CYP3A4 and P-gp

Zavegepant is a substrate for CYP3A4 and P-gp. The applicant conducted a clinical drug interaction study (Study # BHV3500-111) in which Cohort 2 assessed the effect of itraconazole (a strong CYP3A4 and P-gp inhibitor) on the PK of oral and IN zavegepant.

This is an open- label, fixed-sequence study to assess the effect of multiple doses of itraconazole solution on the single dose PK of oral and IN zavegepant in healthy subjects. Subjects (n=18) received a single dose of IN zavegepant 10 mg on Day 1 and a single dose of 50 mg zavegepant oral softgel capsule on Day 3, under fasted conditions and separated by a washout period of approximately 48 hours. On days 4 to 12, the subjects received itraconazole 200 mg QD under fasted conditions. On day 7, 10 mg IN zavegepant was administered under fasted conditions 1 hour after itraconazole dosing. On day 11, 50 mg zavegepant oral soft gel capsule was administered under fasted conditions 1 hour after itraconazole dosing. The PK of zavegepant was characterized when administered alone on Days 1 and 3 and when co-administered with itraconazole on Days 7 and 11.

The summary of pharmacokinetic parameters for IN and oral zavegepant are presented in tables below. Concomitant administration of itraconazole (a strong CYP3A4 and P-gp inhibitor) at steady state with a single dose of 10 mg IN zavegepant showed no clinically relevant changes in the exposure of zavegepant. Based on these results, the applicant proposed that no dose adjustment is necessary when zavegepant is concomitantly administered with CYP3A4 or P-gp inhibitors. The review team agrees with applicant's proposal.

Table 3-3: Summary of zavegepant PK parameters following a single dose of intranasal zavegepant 10 mg alone or co-administration with itraconazole.

Treatment / Day	PK Parameters*		Geometric Mean Ratio (90 % CI)	
	Cmax (ng/mL)	$AUC_{0\text{-}inf}$ (h.ng/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (h.ng/mL)
Zavegepant IN / Day 1	24 (89%)	48 (55%)		
Itraconazole + Zavegepant IN / Day 7	21 (83%)	49 (59%)	0.88 0.64 to 1.20	1.02 0.82 to 1.26

Source: Reviewer confirmed sponsor's analysis. *PK parameters are presented as geometric mean (% CV)

Though the applicant intends to market only 10 mg strength for IN administration, concomitant drug administration of oral soft gel capsules with itraconazole and rifampin were used to inform dosing recommendations for concomitant administration of IN

zavegepant with OATP1B3 or NTCP inhibitors or inducers (discussed in subsequent subsection).

Concomitant administration of itraconazole at steady state with a single dose of 50 mg oral zavegepant capsules resulted in increased exposure of zavegepant (AUC by 59% and Cmax by 77%, respectively (Table 3-3). This suggests the involvement of P-gp and/or CYP3A in the first pass effect.

Table 3-4: Summary of zavegepant PK parameters following a single dose of zavegepant oral softgel capsule 50 mg alone or co-administration with itraconazole.

Treatment / Day	PK Parameters*		Geometric Mean Ratio (90 % CI)	
	Cmax (ng/mL)	$AUC_{0\text{-}inf}$ (h.ng/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (h.ng/mL)
Zavegepant Oral / Day 3	7.2 (151%)	24 (114%)		
Itraconazole + Zavegepant Oral / Day 11	13 (125%)	41 (72%)	1.77 1.09 to 2.89	1.59 1.16 to 2.17

Source: Reviewer confirmed sponsor's analysis. *PK parameters are presented as geometric mean (% CV)

Modulators of OATP1B3 or NTCP

Zavegepant is a substrate for OATP1B3 and NTCP based on in-vitro studies. The applicant conducted a clinical drug interaction study (Study # BHV3500-111), in which Cohort 1 assessed the effect of rifampin (a OATP1B3 and NTCP inhibitor, CYP3A4 and P-gp inducer) on the PK of oral zavegepant.

This was an open- label, fixed-sequence study to assess the effect of multiple doses of rifampin on the single dose PK of oral zavegepant in healthy subjects. Subjects (N=15) received a single dose of zavegepant oral softgel capsule 100 mg on Day 1 under fasted conditions and rifampin 600 mg once daily from Days 2 to 11. On day 11, 100 mg zavegepant oral soft gel capsule was administered under fasted conditions within 5 minutes of rifampin dosing. The summary of pharmacokinetic parameters is presented in table below.

Table 3-5: Summary of zavegepant PK parameters following a single dose of zavegepant oral softgel capsule 100 mg alone or co-administration with rifampin.

Treatment / Day	PK Parameters*		Geometric Mean Ratio (90 % CI)	
	Cmax (ng/mL)	$AUC_{0\text{-inf}}$ (h.ng/mL)	C_{max} (ng/mL)	$AUC_{0\text{-inf}}$ (h.ng/mL)
Zavegepant Oral / Day 1	11 (79%)	40 (72%)		
Rifampin + Zavegepant Oral / Day 11	24 (80%)	91 (73%)	2.17 1.60 to 2.94	2.33 1.80 to 3.02

Source: Reviewer confirmed sponsor's analysis. *PK parameters are presented as geomean (% CV)

The results show that concomitant administration of oral zavegepant with rifampin (at steady-state) resulted in 2.3-fold increase in zavegepant AUC and 2.2-fold increase in Cmax. Based on the in-vitro data, DDI study with itraconazole, and PBPK analyses, the applicant concluded that the main mechanism for the observed increase in zavegepant exposure when co-administered with rifampin is due to the inhibition of both OATP1B3 and NTCP. Based on these results, the applicant recommends (b) (4) The review team disagrees with the applicant's proposal and recommends to avoid use of zavegepant with inhibitors of OATP1B3 or NTCP transporters based on the following considerations:

1. The results of the mass-balance study showed that 80% and 11% of the dose was recovered in feces and urine as unchanged drug, following a single intravenous dose of 5 mg [14C]-zavegepant to healthy males. Further, unchanged zavegepant was found to be most prevalent circulating component, accounting for ~90%, suggesting that the hepatic metabolism of zavegepant was low. Given the involvement of biliary excretion as the major pathway in the elimination of zavegepant, the uptake transporters OATP1B3 and NTCP play an important role in the disposition of zavegepant. The absolute bioavailability of IN zavegepant determined using PPK approach was reported to be 5%.
2. As summarized in Tables 3-3 and 3-4 above, concomitant administration of IN zavegepant and itraconazole did not alter zavegepant exposures, while concomitant administration of oral zavegepant and itraconazole resulted in 60-80% higher zavegepant exposures, suggesting the involvement of CYP3A and/or p-gp in the first-pass effect.
3. The review team notes that the zavegepant exposures following 100 mg oral soft-gel capsules are comparable to those following 10 mg IN zavegepant dose (Study 107: 100

mg oral zavegepant mean $Cmax_{ss}$, 9 ng/mL and mean AUC_{0-24}, 38 ng•h/mL ; Study 102: 10 mg IN zavegepant mean $Cmax_{ss}$, 13 ng/mL and mean AUC_{0-24}, 33 ng•h/mL).

4. Rifampin is a strong inducer of CYP3A and P-gp, and an inhibitor of OATP1B3 and NTCP. Therefore, the (up to 2.3-fold) increase in zavegepant exposures is a composite effect of induction of CYP3A and P-gp (which is supposed to decrease zavegepant exposures), and inhibition of OATP1B3 and NTCP (which is supposed to increase zavegepant exposures).
5. Therefore, observed 2.3-fold increase in zavegepant exposures following 100 mg oral zavegepant and steady-state rifampin was likely an underestimate of inhibition of OATP1B3 and NTCP.
6. The applicant claimed that rifampin (at steady-state) is a weak NTCP inhibitor, and the observed increase in zavegepant exposures is likely driven by primarily by OATP1B3. However, the review team notes that the design of the DDI study between oral zavegepant and rifampin makes it difficult to delineate the relative contribution of induction of CYP3A and p-gp, and/or of inhibition of OATP1B3 and NTCP. Furthermore, the relative contribution of OATP1B3 and NTCP in the disposition of zavegepant is not clear.
7. Additionally, the applicant conducted PBPK modeling and simulation under two scenarios and the results are summarized below:
    a. Concomitant administration of single dose of IN zavegepant and single oral dose of rifampin is predicted to result in 2.39-fold increase in AUC and 1.70-fold increase in Cmax.
    b. Cyclosporine (CsA) is a dual inhibitor of OATP1B3 and NTCP. Concomitant administration of single dose of IN zavegepant and single oral dose of CsA is predicted to result in up to 1.58-fold increase in zavegepant exposures, assuming a ratio of 90:10 for the relative contribution of OATP1B3: NTCP mediated uptake and upto 1.37-fold increase in zavegepant exposures, assuming a ratio of 50:50 for the relative contribution of OATP1B3: NTCP mediated uptake of zavegepant.
8. The review team notes that the results in #7a above clearly exceed the 2-fold safety margin (relative to 10 mg IN zavegepant dose). The applicant intends to market a single dose strength of 10 mg, and therefore, lack of availability of lower dose strength precludes from adjusting zavegepant dose.
9. The complex interplay of the DDI mechanisms and lack of clear understanding of the relative contributions of OATP1B3 and NTCP transporters in disposition of zavegepant (as outlined in #6 above), contribute to uncertainties in magnitude of interaction reported by CsA PBPK model (outlined in #7b). Furthermore, the review

team notes that CsA PBPK model (outlined in #7b) was verified with repaglinide, which is suggested to be a substrate for both OATP1B1 and OATP1B3. The current data does not offer insights into definitive contribution of OATP1B1 versus OATP1B3 on the disposition of repaglinide. The Ki of 0.032 μM for OATP1B3 used in CsA PBPK model was not independently verified with clinical data. Therefore, uncertainty exists in the predicted magnitude of the effect of cyclosporine on OATP1B3-specific pathway, and consequently adds to the overall uncertainty in the PBPK prediction which assumed the relative contributions of OATP1B3 and NTCP.

10. In summary[2], an increase of more than 2-fold in zavegepant exposures with concomitant administration of IN zavegepant and OATP1B3 or NTCP inhibitors cannot be completely ruled out.

The applicant did not conduct drug-interaction studies to evaluate the impact of OATP1B3 or NTCP inducers on zavegepant exposures. Although the inducibility of OATP1B3 or NTCP and associated clinical implications have not been well established, such a possibility cannot be completely ruled out based on literature[3]. Therefore, the review team recommends to avoid concomitant use of zavegepant with inducers of OATP1B3 or NTCP

Intranasal Decongestants

Intranasal decongestants may decrease the absorption of concomitantly administered nasal products (the evidence in literature shows mixed results). The review team recommends to avoid concomitant administration of intranasal decongestants with zavegepant. If concomitant use cannot be avoided, intranasal decongestants should be administered at least 1 hour after zavegepant administration. This 1-hour interval is consistent with Tmax of IN zavegepant (0.5 to 1 hour).

Oral Contraceptives

Ethinyl estradiol-levonorgestrel (EE-LNG) is a combined oral contraceptive drug and CYP3A4 is involved in the metabolic pathway of EE and LNG. The applicant conducted DDI study (BHV3500-109) to characterize the potential of zavegepant as a perpetrator to affect the disposition of oral contraceptives.

Study BHV3500-109 was an open-label, multiple-dose, fixed-sequence, 2-period, DDI study in healthy females. Subjects (n=26) received multiple doses of IN zavegepant (20 mg) and a single dose of EE-LNG (0.02 mg-0.10 mg) under fasted conditions in 2 periods, with a washout period of at least 7 days between the periods.

---

[2] Correspondence between the Agency and applicant are included in sequence numbers 0035 (13 February 2023), 0036 (17 February 2023), 0037 (23 February 2023), 0038 (27 February 2023).

[3] Zamek-Gliszczynski MJ et al, Clin Pharmacol Ther. 2021, 109: 55-64)

Co-administration of zavegepant IN with EE-LNG did not show a clinically significant change in EE and LNG exposures. Therefore, the applicant proposed that oral contraceptives may be co-administered with IN zavegepant. The review team agrees with the applicant's proposal.

Sumatriptan

The applicant conducted a clinical drug interaction study (Study # BHV3500-110) to assess the effect of zavegepant administration on the PK and pharmacodynamics (resting BP) of sumatriptan.

This was a single center, randomized, partially blinded, placebo-controlled, one-arm study. On days 1 and 4, subjects received 12 mg single dose of sumatriptan open-label (administered as 2 subcutaneous injections - 6 mg/0.5 mL separated by 1 h; n=42). The zavegepant 10 mg IN or placebo administered as 2 sprays of 0.1 mL (one spray in each nostril) for a total dose of 20 mg from Days 2 to 4 (3 days). On Day 4, zavegepant or placebo was administered immediately after the second sumatriptan injection. Blood samples for intensive sumatriptan and zavegepant PK were collected on Day 1 and Day 3, respectively, and again on Day 4 for both drugs. Ambulatory BP monitoring was used to obtain BP recordings predose and over a 13-hour period at predetermined time points after the first sumatriptan injection on Days 1 and 4 and zavegepant or placebo administration on Day 3. The results of the study indicated that the concomitant administration of sumatriptan (single dose) with zavegepant (multiple doses) did not affect the PK of each other. In addition, no clinically significant differences were observed in the time-weighted average of mean arterial pressure between 2 treatments.

In-vitro Metabolism Studies

Inhibitor/Inducer:

In-vitro studies showed that zavegepant is not an inhibitor of CYP1A2, 2C9, 2C19, 2B6 2D6 and 3A4. It is not a time- dependent inhibitor of CYP2C9, 2C19, 2D6, 2B6, 2C8, and 3A4. In-vitro studies indicated that zavegepant showed little to no induction of CYP1A2, 2B6, or 3A4/5.

In-vitro Transporter Studies

As a Substrate:

In vitro human transporter studies (Studies XT178113, XT178116 and BioHaven-01) indicated that zavegepant is a substrate for P-gp, MATE1, MATE2-K, OATP1B3 and NTCP transporter, and not a substrate of BSEP, BCRP, OATP1B1, OAT1, OAT3, OCT2, BSEP, MRP2, MRP3, or MRP4 transporters. The clinical relevance of potential interactions with these transporters are summarized below:

- *Substrate for P-gp*: The concomitant administration of itraconazole (a strong CYP3A4 and P-gp inhibitor) at steady state with a single dose of 10 mg IN zavegepant showed

no clinically relevant changes in the exposure of zavegepant. Hence a clinically relevant drug interaction effect of CYP3A4 and P-gp inhibitors on zavegepant exposure is not expected.

- *Substrate for MATE1, MATE2-K:* These transporters are primarily expressed in the kidneys. The renal route plays a minor role in the clearance of zavegepant (10%). Therefore, no clinical drug interactions are expected when co-administered with MATE1, and MATE2-K inhibitors.
- *Substrate for OATP1B3 and NTCP*: Concomitant administration of rifampin (inhibitor of both OATP1B3 and NTCP) increased exposure of zavegepant (AUC by 2.3-fold & Cmax by ~2.2-fold). The details of this drug interaction and its labeling recommendations are provided in the Section 3.3.3 above.

As an Inhibitor

Zavegepant is not an inhibitor of P-gp, BCRP, OAT1 and OAT3 (IC50 ≥ 100 µM); OATP1B1 and OATP1B3 (IC50 ≥ 50 µM). It showed a potent inhibition of OCT2, MATE1 and MATE2-K with IC50 values of 2.15, 0.158, and 4.96 µM, respectively. Considering the peak concentrations for 10 mg IN daily dosing (Cmax, 0.0203 µM) and protein binding (~90%), clinically relevant drug interactions are not expected (for the lowest IC50 value 0.158 µM, the Imax,u/IC50 is ≤ 0.013, much less than 0.1). The details are provided below.

- An investigational drug has the potential to inhibit transporter in vivo to cause clinical DDI if the Imax,u/IC50 value is ≥ 0.1 (where Imax,u: maximal unbound plasma concentration of the interacting drug at steady state). The calculations using Cmax (12.98 ng/mL= 0.0203 µM, Molecular weight: 639 Da) of zavegepant 10 mg IN multiple dose value in humans (Study BHV3500-102), Imax,u/IC50 value is much less than 0.1 (Imax,u/IC50, ~0.013 for the lowest IC50 value of 0.158 µM). Hence a clinically relevant drug interactions due to inhibition of OCT2, MATE1 or MATE2-K by zavegepant are not expected.

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support approval of the to-be-marketed formulation?

Yes. The zavegepant nasal spray is a solution of 10 mg zavegepant free base (equivalent to (b) (4) mg of zavegepant hydrochloride) in a buffered aqueous solution. The composition of the formulation and design of the device used during the clinical trials remained unchanged and the same are proposed for commercial use (to-be-marketed). Therefore, no PK bridging studies are required.

4. Appendices

4.1 Summary of Bioanalytical Method Validation

For the determination of zavegepant concentrations in human plasma, the applicant used validated high- or ultra- performance liquid chromatographic (HPLC/UPLC) methods with tandem mass spectrometry detection methods. Plasma samples containing EDTA as an anticoagulant and internal standard were processed using liquid extraction prior to LC-MS/MS analysis. The internal standard is Zavegepant-d8. For the mass balance study, total radioactivity concentrations in plasma, whole blood, urine, and feces were determined using liquid scintillation counting (b) (4)

- Clinical site: inVentiv Health Clinique Inc. (a Syneos Health Company) 1951 NW 7th Avenue, Suite 450 Miami, FL 33136, USA
- Bio-analytical sites
    - Mass balance study, BHV3500-104: (b) (4)
    - For all other studies: (b) (4)

Summary of bioanalytical methods used in the clinical program is provided in Table 4-1.

Table 4-1: Summary of bioanalytical methods utilized in clinical studies of zavegepant

Analytical Study Number	Range	Accuracy (Mean % Deviation from Nominal) Within Run Between Run	Precision (CV%) Within Run Between Run	Incurred sample reanalysis % (ISR) Passing/Number of Samples	Clinical Studies Supported by Method
182006ASZR	0.4-400 ng/mL	-8.20 to 1.30 -4.96 to 2.18	2.14 to 4.96 3.62 to 5.08	99.1% of 113 samples	BHV3500-101
180448-Amendment II	0.4-200 ng/mL	-6.80 to 0.70 -4.96 to 2.18	0.90 to 2.91 3.62 to 5.08	98.8% of 170 samples	BHV3500-102
BHV/04	0.4 -200 ng/mL	-0.8 to 8.3 2.0 to 4.2	1.3 to 5.3 3.1 to 5.8	95.0% of 20 samples	BHV3500-104
202002AXAI	40 – 50,000 pg/mL	-2.96 to 5.00 0.85 to 3.47	0.92 to 4.04 1.61 to 6.44	97.4% of 117 samples	BHV3500-105
202013AYFGAYFJ (Part 1)				92.0% of 50 samples	BHV3500-108
200316AYMUAYSO-	20 – 50,000	-2.20 to 6.39	0.98 to 7.80	100% of 72	BHV3500-

AZAK	pg/mL	0.85 to 3.47	1.61 to 6.44	samples	109
200320AYMZAYRK				98.3% of 116 samples	BHV3500-110
200406AYZF				97.1% of 140 samples	BHV3500-111

For all studies, the cumulative accuracy (% bias) was less < ± 15% and precision (%CV) was < 15% for QC samples and calibration curves used the LC-MS/MS bioanalytical assay. The results of incurred samples reanalysis were within acceptable limits.

Reviewer's Comments:

The bioanalytical method used in analysis of pharmacokinetic samples of zavegepant fulfill the required criterion for 'method validation' and 'application to routine analysis' provided in the 'Guidance for Industry: Bioanalytical Method Development' and is acceptable.

4.2 Pharmacometrics Review

Applicant's Analysis

Population PK Analysis

The final PopPK model was developed from a dataset of 10819 evaluable Zavegepant plasma concentrations from 594 subjects enrolled in 10 Phase 1 single and multiple dose studies. A nonlinear mixed effects modeling approach with the first-order conditional estimation with interaction (FOCEI) method in NONMEM, version 7.2 (ICON, Hanover, MD) was used for the PopPK analysis.

Table 1. Summary of Studies Included in the PopPK Analysis

Protocol	Title	Subject Population	No. of Subjects	Dose
BHV3500-101	Phase 1 SADs study to evaluate the safety and tolerability	Healthy subjects	43	1,3,5,10,20, and 40 mg IN
BHV3500-102	Phase 1, randomized, double-blind, placebo-controlled MAD study	Healthy subjects	36	5,10,20 mg QD x14d, 20mg 2hx8d IN
BHV3500-104	Single-dose study to assess the mass balance recovery, ADME	Healthy male subjects	6	5 mg IV infusion
BHV3500-105	Phase 1, randomized, open-label, fixed-sequence, 2-period, comparative BA study during a migraine attack vs a non-migraine period	Migraine subjects	39(38 for PD)	10,20 mg IN
BHV3500-106	Phase 1, open-label, 8-week, safety study of oral zavegepant	Migraine subjects	317	100 mg capsules, oral
BHV3500-107	Phase 1, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability and food effect	Healthy subjects	47	50,100mg capsules, oral
BHV3500-108	Phase 1, open-label, single-dose study to evaluate the effects of moderate hepatic impairment on the PK of	Healthy subjects and subjects with moderate hepatic impairment	16	10 mg, IN

	zavegepant IN			
BHV3500-109	Phase 1, open-label, fixed-sequence study to evaluate the effects of multiple-dose administration of zavegepant IN on oral contraceptive	Healthy female subjects	25	20 mg, IN
BHV3500-110	Phase 1, randomized, partially blind, placebo-controlled study to evaluate the effects of zavegepant and concomitant sumatriptan on blood pressure	Healthy adult subjects	34	20mg, IN
BHV3500-111	Phase 1, open-label, fixed-sequence, DDI study to evaluate the effects of rifampin on the PK of oral zavegepant and the effects of itraconazole on the PK of oral and IN zavegepant	Healthy subjects	31	20,50,100 mg, IN

Source: Adapted from applicant's PopPK report BIOH-PMX-VAZEGEPANT-3358, Page 12, Table 1

Table 2: Summary of Baseline Demographic Data in the Primary Analysis: Continuous Variables

Covariate (Unit)	**Overall (N=277)**	
	Mean (Std Dev)	Median [Min, Max]
Age (years)	40.5 (11.4)	40.0 [18.0, 71.0]
Body weight (kg)	74.8 (11.9)	74.2 [49.2, 131]
Body mass index (kg/m^2)	26.2 (3.08)	26.0 [18.6, 37.8]
Albumin (U/L)	4.47 (0.297)	4.50 [3.50, 5.20]
Alkaline phosphatase (U/L)	68.7 (17.6)	67.0 [29.0, 134]
Alanine aminotransferase (U/L)	19.6 (9.82)	17.0 [4.00, 77.0]
Aspartate aminotransferase (U/L)	19.4 (7.42)	18.0 [9.00, 82.0]
Bilirubin (mg/dL)	0.488 (0.197)	0.468 [0.175, 1.60]

Serum creatinine (mg/dL)	0.840 (0.178)	0.836 [0.486, 1.30]
Creatinine clearance (mL/min)	117 (23.5)	115 [52.5, 211]

Source: Adapted from applicant's PopPK report BIOH-PMX-VAZEGEPANT-3358, Page 24, Table 4

Table 3: Summary of Baseline Demographic Data (N=277) in the Primary Analysis: Categorical Variables

Covariate	Levels	N (Percentage)
Sex	Female	126 (45.5%)
	Male	151 (54.5%)
FED status	Fasting	22(7.94%)
Route of administration	Intranasal	209 (75.5%)
	Intravenous	6 (2.2%)
	Oral	62 (22.4%)
Race	Black/African American	32 (11.6%)
	White	245 (88.4%)
Ethnicity	Hispanic or Latino	159 (57.4%)
	Others	118 (42.6%)
Hepatic impairment	Moderate	8(2.88%)
Co-treated with rifampicin	Yes	15 (5.42%)
Co-treated with oral contraceptives	Yes	25 (9.03%)
Co-treated with sumatriptan	Yes	35 (12.6%)
Co-treated with itraconazole (intranasal route)	Yes	18 (6.49%)
Co-treated with itraconazole (oral route)	Yes	18 (6.49%)

Source: Adapted from Applicant's PopPK report BIOH-PMX-VAZEGEPANT-3358, Page 24, Table 5

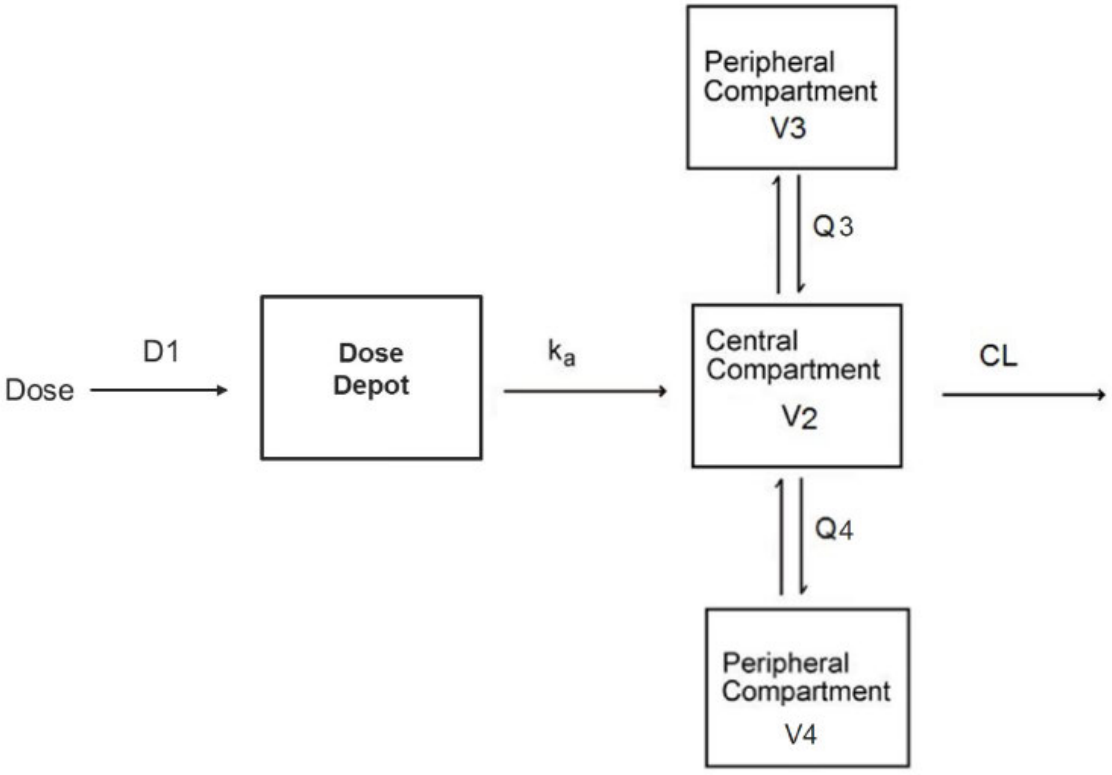
PopPK Model

A PopPK approach was used to evaluate the PK of zavegepant in normal healthy

subjects and migraine patients. A combined PopPK model was developed using different zavegepant formulations, i.e. IV, IN, and oral soft gelatin capsule formulations. The analysis was performed using 9 studies with intensive PK sampling and 1 study (BHV3500-10616) where sparse PK plasma concentration data was collected after oral dosing.

The final PopPK model comprised of 3 compartments along with sequential zero and first oral absorption, as illustrated in **Figure 1**. Inter-individual variability was estimated for the elimination clearance, central volume of distribution, absorption rate constant, duration of absorption, peripheral volume, and bioavailability. An additive and proportional residual error model was utilized.

Figure 1: Schematic Representation of the Zavegepant PopPK Model



Abbreviations: CL=clearance; D1=duration of absorption; ka=absorption rate constant; PPK=population pharmacokinetic; Q3=clearance to first peripheral compartment; Q4=clearance to second peripheral compartment; V2= central volume of distribution; V3= first peripheral volume of distribution; V4= second peripheral volume of distribution

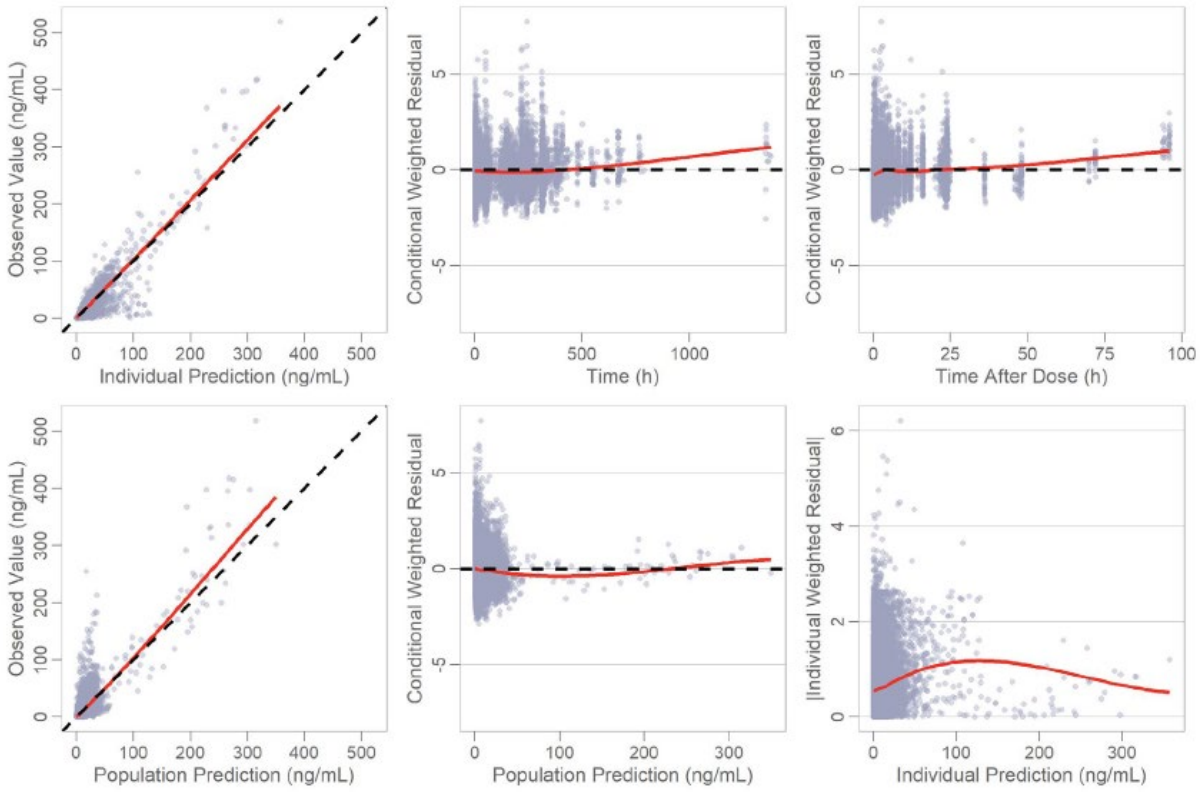
Source: Applicant's PopPK report BIOH-PMX-VAZEGEPANT-3358, Page 27, Figure 2

The PopPK model was parameterized in terms of clearance (CL), volume of the central compartment (V2), intercompartment clearance of compartment 2 (Q3), peripheral volume of distribution of compartment 2 (V3), inter-compartment clearance of compartment 3 (Q4), peripheral volume of distribution of compartment 3 (V4), the

duration of the zero-order absorption (D1), and first-order absorption rate constant (ka) for IN administration.

The model building was performed in a stepwise manner. Study BHV3500-104, with richly sampled IV data, was first modeled. Next, the studies with other formulations were added to the analysis data and model. In order to account for the IN and oral administration route in the base model, a scaling factor was added to the V2. Data from Study BHV3500-106 was sparse and had a destabilizing impact on the model. The popPK model was therefore built with 9 of the 10 studies. After the final PopPK model was defined, Study BHV3500-106 subjects were fitted with the final model parameters fixed but allowing interindividual fitting of the BHV3500-106 data. Allometric scaling with body weight was applied to the disposition parameters. Covariate selection was performed through iterative testing of potential covariate effects. The final PopPK model zavegepant was assessed with diagnostics plots including goodness-of-fit (**Figure 2**) and pcVPC (**Figure 3**).

Figure 2: General Goodness-of-Fit Plots for Zavegepant from the Final PopPK Model



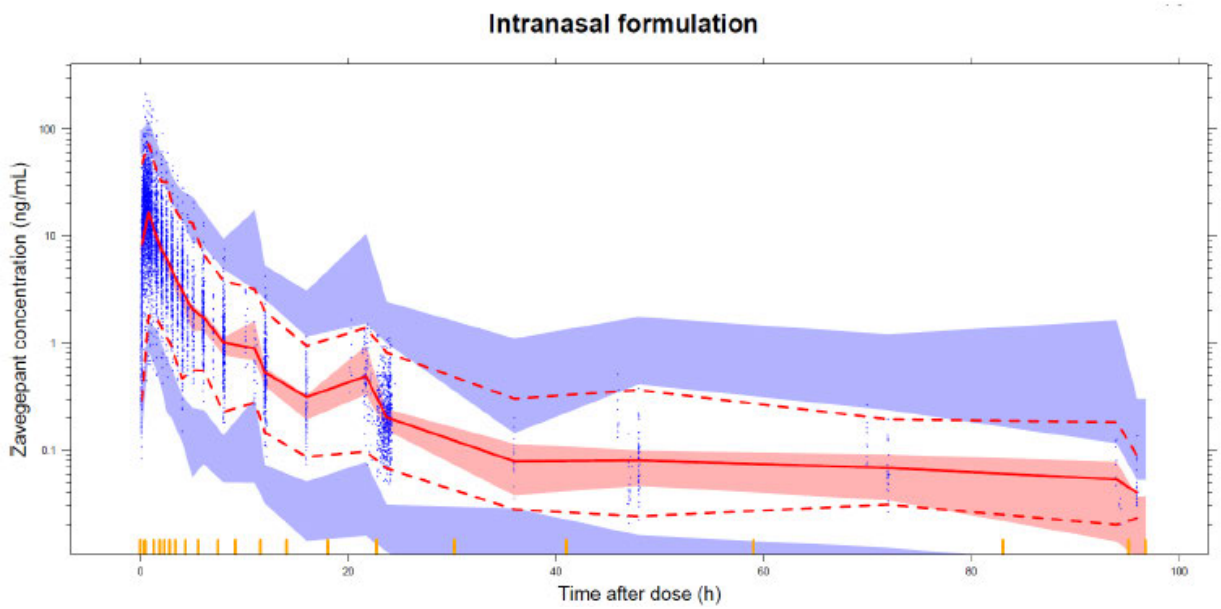
Notes: The black dashed line is the identity line. The red line represents the LOESS smooth

Abbreviations: LOESS=locally estimated scatterplot smoothing; PopPK=population

pharmacokinetic

Source: Applicant's PopPK report BIOH-PMX-VAZEGEPANT-3358, Page32, Figure 4

Figure 3: Prediction-corrected Visual Predictive Check for the Final popPK Model for Zavegepant



Notes: The solid line represents the median of the observed data. Shaded regions encompass 90% of the simulated (N=500) values of the predicted medians and the 5th and 95th percentiles. Data points represent the prediction-corrected observed data.

Abbreviations: N=number of subjects; PopPK=population pharmacokinetic

Source: Applicant's PopPK report BIOH-PMX-VAZEGEPANT-3358, Page33, Figure 5

Parameter estimates from the final PopPK model are presented in **Table 4**. For a typical patient with body weight of 70 kg, the estimated CL was 13.3 L/h, V2 was 12.1 L, Q3 was 2.65 L/h, V3 was 65.9 L, Q4 was 5.19 L/h, V4 was 10.7 L, Ka and D1 for IN administration was 5.79 /h and 0.144 h, respectively.

Statistically significant covariates were identified in the final model as: 1) moderate hepatic impairment on clearance, 2) itraconazole administration on clearance when zavegepant was administered orally, and 3) rifampin administration on the clearance of orally administered zavegepant. It is noteworthy that a covariate effect of itraconazole administration on zavegepant clearance was statistically insignificant when zavegepant was administered IN. Other covariates including age, race, ethnicity, sex, renal impairment (CLcr), oral contraceptives, and sumatriptan, were found not to be significant in modeling zavegepant exposure.

Table 4: Summary Statistics of Parameter Estimates for the Final PopPK Model

Parameter (Unit)	Estimate	%RSE	%IIV (%RSE) [%Shrinkage]
NONMEM Model Estimates			
CL (L/h)	13.3	9.9%	26.8% (6.1%) [17.8%]
V2 (L)	12.1	8.8%	32.2% (10.9%) [28%]
V3 (L)	65.9	10.7%	26.1% (23.1%) [49.9%]
Q3 (L/h)	2.65	10.5%	-
V4 (L)	10.7	10.1%	-
Q4 (L/h)	5.19	16.3%	-
Bioavailability of intranasal formulation (%)	5.12	11%	66.1% (4.8%) [6.8%]
Bioavailability of oral formulation (%)	0.649	17.5%	
ka for intranasal formulation (1/h)	5.79	5.1%	44% (11%) [41.1%]
ka for oral formulation (1/h)	0.81	6.1%	
Duration of absorption for intranasal formulation (h)	0.144	8.73%	114.5% (7.7%) [11.6%]
Duration of absorption for oral formulation (h)	0.954	14.4%	
Fed status on bioavailability	-50.9%	9.8%	-
Scaling factor on volume of distribution for intranasal formulation	+110%	7.4%	-
Scaling factor on volume of distribution for oral formulation	17.2%	87%	-
Itraconazole use on CL when administered orally	-27.9%	26.3%	-
Moderate hepatic impairment on CL	-43.9%	13.5%	-
Rifampicin on CL	-41.1%	12.1%	-
Additive error (ng/L)	0.001 FIX	-	-
ıal error (%)	7.8%		

Source: run8134a.lst

Notes: CL, Q3, and Q4 parameters have body weight exponents fixed to 0.75, and V2, V3, and V4 have body weight exponents fixed to 1.0 (allometry).

For the purposes of the model table, clearance (CL, Q3, and Q4) and volume of distribution (V2, V3, and V4) parameters are shown for IV formulation (F=100%).

Abbreviations: %IIV=percentage of the interindividual variability; %RSE=percentage of the relative standard error; CL=clearance; IV=intravenous; ka=absorption rate constant; NONMEM=nonlinear mixed-effects modeling software; PPK=population pharmacokinetic; Q3=clearance to first peripheral compartment; Q4=clearance to second peripheral compartment; V2=central volume of distribution; V3=first peripheral volume of distribution; V4=second peripheral volume of distribution; F= bioavailability.

Source: Applicant's PopPK report BIOH-PMX-VAZEGEPANT-3358, Page30-31, Table 7

Reviewer's Analysis

Methods

Data Sets

Data set used is listed in **Table 5**.

Table 5: Analysis Data Sets

Datasets

Study	Name	Link to EDR
Study BHV3500-101,102,104,105, 106,107,108,109, 110 and 111	ppkdata.csv	\\CDSESUB1\EVSPROD\nda216386\0001\m5\datasets\bioh-pmx-vazegepant-3358\analysis\adam\datasets\ppkdata.csv

Software

PopPK model fitting was performed in NONMEM 7.3.0 and Pirana 2.9.9. Primary analysis and plotting were performed in R 4.1.2.

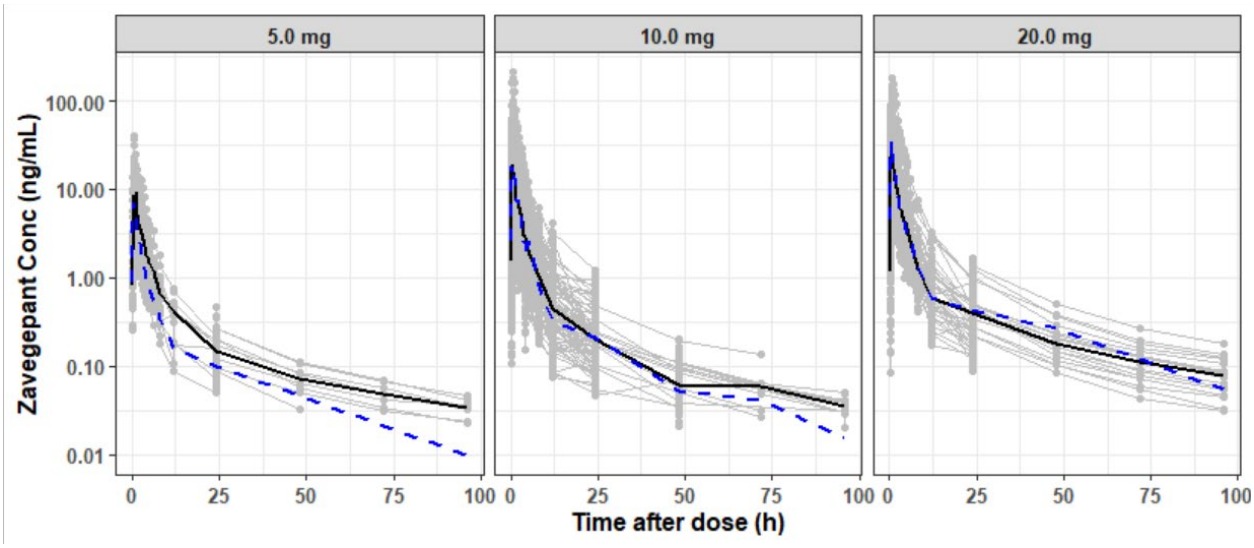
Results

The reviewer was able to reproduce the applicant's PopPK results with NONMEM (version:7.3.0). The applicant's PopPK analysis appears adequate for characterizing the PK profiles for zavegepant. No additional modeling analysis was conducted.

Overview of Observed Data

Figure 4 presents PK profiles of zavegepant for subjects at 5 mg/day, 10 mg/day and 20 mg/day dose level.

Figure 4: Observed Zavegepant Concentration vs. Time after Dose for 5, 10 and 20 mg/day Doses in Subjects in Study BHV3500-101, 102, 105, 108, 109, 110 and 111

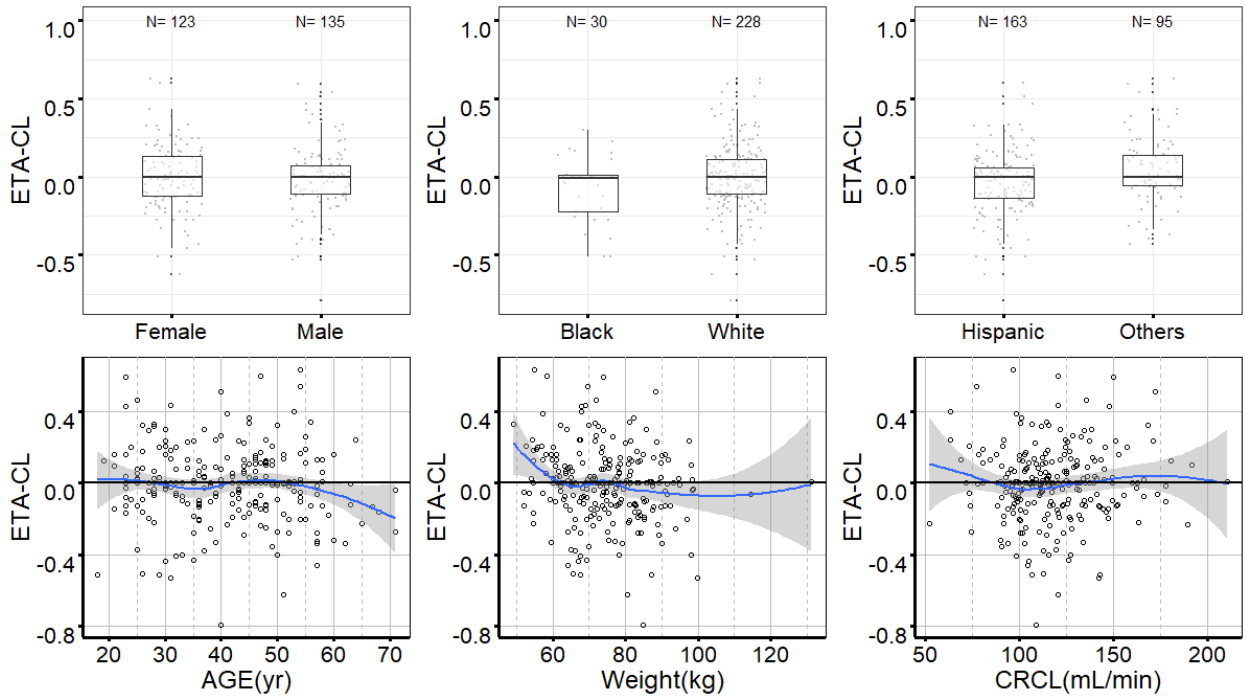


Note: Observed values are indicated by solid grey circles, the black solid lines represent the observed medians, and the blue dashed lines represent the population predicted medians.

Source: Reviewer's Analysis

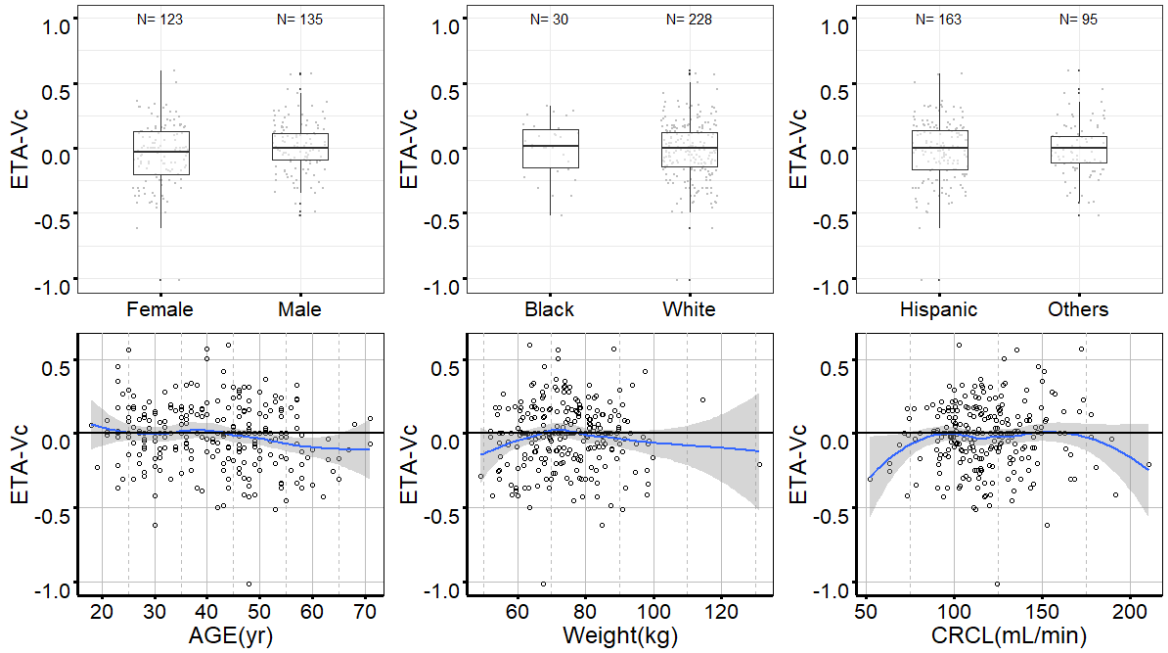
The impact of sex, race, ethnicity, age (18-71 years), bodyweight (49-131kg), CLcr (52 to 210 mL/min) on the PK of zavegepant were investigated. No clear trends in ETA with these covariates were observed with bodyweight allometric scaling in the final PopPK model (**Figure 5**, **Figure 6** and **Figure 7**). Therefore, after inclusion of body weight in the PopPK model, other covariates were not found to influence PK of zavegepant.

Figure 5: Individual Random Effects versus Covariates Plots for Clearance of Zavegepant



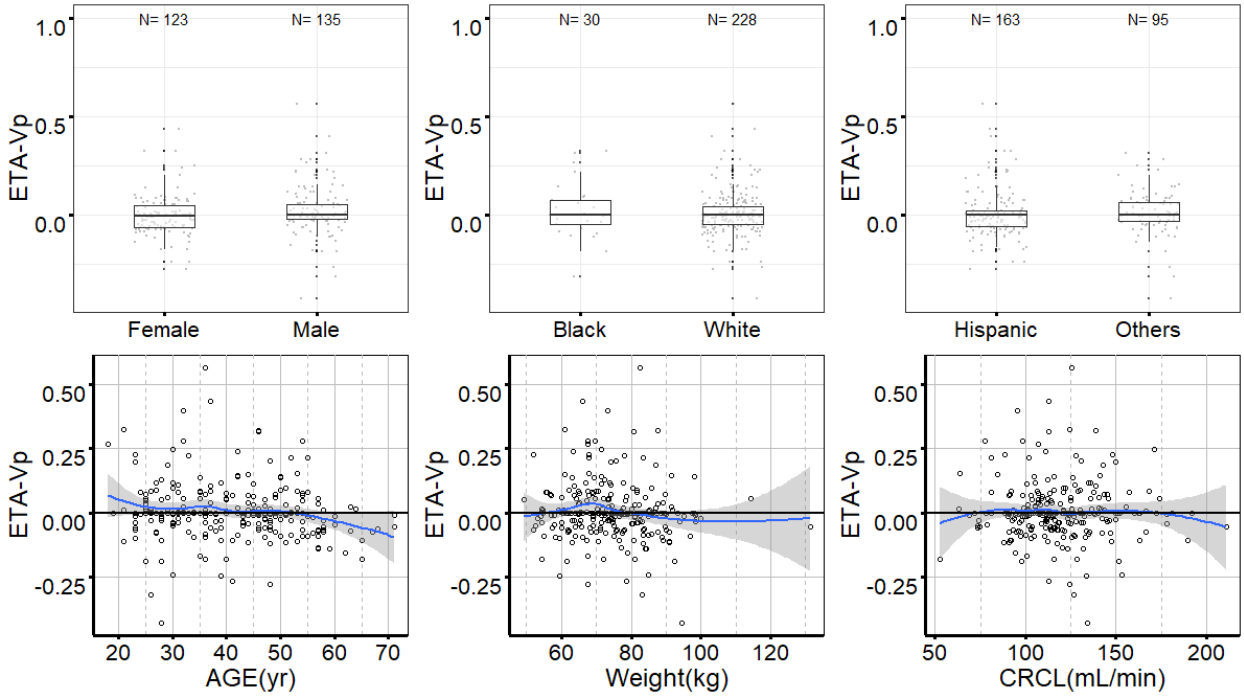
Source: Reviewer's Analysis

Figure 6: Individual Random Effects versus Covariate for Central Volume of Distribution (V2) of Zavegepant



Source: Reviewer's Analysis

Figure 7: Individual random effects versus Covariates Plots for Peripheral Volume of Distribution (V3) of Zavegepant



Source: Reviewer's Analysis

Listing of Analyses Codes and Output Files

File Name	Description	Location
Zavegepant pk analysis.R	PK and PopPK analysis file	\\Review\2022\NDA 216386 Zavegepant\PPK analysis\Reviewer\Rscript

Reviewer's Comments:

The applicant's popPK analysis appears adequate for describing the PK of zavegepant after intranasal administration. The general statement regarding PK of zavegepant in the label (Section 12.3) is appropriate.

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/

SURESH B NARAHARISETTI
03/06/2023 02:39:44 PM

JIE LIU
03/06/2023 02:56:11 PM

VENKATESH A BHATTARAM
03/06/2023 04:35:07 PM

YUCHING N YANG
03/06/2023 04:49:03 PM

GOPICHAND GOTTIPATI
03/06/2023 07:55:29 PM

MEHUL U MEHTA
03/07/2023 07:46:21 AM