CENTER FOR DRUG EVALUATION AND RESEARCH

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CLINICAL REVIEW(S)

CLINICAL REVIEW

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Established/Proper Name	Zavegepant
(Proposed) Trade Name	Zavzpret
Applicant	Pfizer Inc
Dosage Form(s)	Nasal Spray
Applicant Proposed Dosing Regimen(s)	Single dose of 10 mg nasal spray; Maximum dose in 24-hours period of 10 mg
Applicant Proposed Indication(s)/Population(s)	Acute treatment of migraine
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Acute treatment of migraine with or without aura in adults

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Zavegepant (formerly BHV-3500 and vazegepant) nasal spray is an intranasally administered, small molecule, calcitonin gene-related peptide (CGRP) receptor antagonist. Zavegepant is a new molecular entity (NME). Zavegepant is a combination product consisting of the aqueous solution formulation of zavegepant and a nasal spray device (b) (4) (b) (4) CGRP is thought to have a role in the pathophysiology of migraine. CGRP is a potent vasodilator in the cerebral, coronary, and renal vasculature and has been shown to increase during an acute migraine attack (Edvinsson et al 2019). In addition, migraine-like headaches have been induced by CGRP infusion in migraine patients (Hansen et al 2010).

The applicant has proposed a dose for marketing of one 10 mg spray given intranasally into one nostril with a maximum dose of 10 mg in a 24-hour period. A single dose of 10 mg was evaluated in both pivotal, clinical, efficacy studies. The intended indication for Zavegepant is the acute treatment of migraine with or without aura in adults.

At the time of this review, there are two FDA-approved, orally administered, small molecule CGRP receptor antagonist for the acute treatment of migraine: ubrogepant and rimegepant. Rimegepant is also approved for the preventive treatment of episodic migraine. Atogepant (another orally administered, small molecule CGRP receptor antagonist) is FDA-approved for the indication of the preventive treatment of episodic migraine in adults. In addition, erenumab, fremanezumab, galcanezumab, and eptinezumab, are four FDA-approved monoclonal antibodies that act on the CGRP pathway for the preventive treatment of migraine.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant has submitted substantial evidence of effectiveness for zavegepant 10 mg nasal spray. The applicant has provided data from two adequate and well-controlled studies, which demonstrate that zavegepant is effective for the acute treatment of migraine with or without aura by utilizing the co-primary endpoints of pain freedom at 2 hours postdose and most bothersome symptom (MBS) at 2 hours postdose. Both pivotal studies used a nasal spray formulation of zavegepant as compared to placebo. In one of the pivotal trials, multiple key secondary endpoints were found to be statistically significant and supportive of the co-primary endpoints. Those key secondary endpoints included pain relief at 2 hours, return to normal function at 2 hours, sustained pain freedom from 2 to 48 hours, freedom from photophobia at 2 hours, and freedom from phonophobia at 2 hours. Therefore, I recommend approval of zavegepant 10 mg nasal spray for the acute treatment of migraine with or without aura in adults.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Zavegepant is a small molecule, calcitonin gene-related peptide (CGRP) receptor antagonist. The proposed indication for zavegepant is for the acute treatment of migraine with or without aura in adults. Zavegepant is a combination product consisting of the aqueous solution formulation of zavegepant and a nasal spray device. Zavegepant was evaluated in clinical trials as a nasal spray. Zavegepant is administered as a single 10 mg nasal spray with no more than one spray in a 24-hour period.

Migraine is a common, chronic, neurologic disorder that can be a serious and a potentially disabling condition affecting patient's quality of life. The severity and frequency can vary, with patients typically experiencing recurrent, moderate to severe headaches. There are multiple FDA-approved therapies for acute treatment of migraines such as triptans, ergots, CGRP receptor antagonists, and NSAIDs. Zavegepant nasal spray may offer a practical advantage to some patients by delivering the drug product through a nasal spray rather than orally.

Two trials were used to demonstrate the efficacy of zavegepant. One of the trials was a dose-finding trial, and the other trial utilized a single dose-level based on the findings of the other pivotal trial. Both studies evaluated the effect of a single dose of zavegepant on a single migraine attack of moderate or severe intensity. There was no option to use a second dose of zavegepant in these two trials. The co-primary endpoints of pain freedom at 2 hours postdose and most bothersome symptom (MBS) at 2 hours postdose, were used in the two pivotal trials. Both co-primary endpoints were found to be clinically meaningful and concurred with the Guidance for Industry, "Migraine: Developing Drugs for Acute Treatment". Both trials demonstrated statistical significance of the 10 mg dose for both co-primary endpoints. Overall, 7-8% and 9% more zavegapant-treated patients experienced pain freedom at 2 hours postdose and MBS freedom at 2 hours postdose, respectively, compared to placebo-treated patients.

The zavegepant safety profile was evaluated through two pivotal controlled studies, and an open-label, long-term safety, study with repeat dosing. In addition, an 8-week hepatotoxicity study was conducted, that involved healthy subjects who received the 100 mg oral formulation of zavegepant daily. There were no major toxicities identified in these trial. In the double-blind, controlled, clinical trials, adverse events that occurred in at least 1% of zavegepant-treated patients were taste disorder, nausea, nasal discomfort, vomiting, throat irritation, nasal congestion, and fatigue/somnolence. In the open-label study, adverse events that occurred in at least 3% of zavegepant-treated patients were taste disorder, nasal discomfort, COVID-19, nasal congestion, nausea, throat irritation, back pain, pyrexia, myalgia, rhinorrhea, arthralgia, abnormal liver function tests, abdominal pain/dyspepsia, oropharyngeal discomfort, and fatigue/somnolence.

Postmarketing requirement (PMR) for a pregnancy registry and outcome study, and the required Pediatric Research Equity Act (PREA) PMRs for

the study of pediatric migraine, are recommended. I also recommend enhanced pharmacovigilance for stroke, myocardial infarction, and hepatotoxicity to address risks associated with zavegepant in the postmarketing setting.

I recommend the approval of zavegepant 10 mg nasal spray for the acute treatment of migraine with or without aura in adults. Overall, the efficacy of zavegepant appears to be similar to other products for the acute treatment of migraines in adults. The tolerability appears to be similar to other nasal sprays used for the acute treatment of migraine.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Migraine is a common, chronic, neurologic disorder. • Migraine is characterized by recurrent, moderate to severe headaches. • Migraine attacks typically are unilateral headaches associated with other symptoms, such as nausea, vomiting, phonophobia, or photophobia. • Minor physical activity can exacerbate headaches, which may last from 4 to 72 hours. • A migraine with aura is typically characterized by symptoms of visual, sensory, language, or brainstem dysfunction associated disturbances lasting between 5-60 minutes before onset of headache.	Migraine significantly affects patients' ability to perform daily activities. Migraine can be a serious and potentially disabling condition affecting the patient's quality of life.
Current Treatment Options	• There are multiple FDA-approved therapies for acute treatment of migraines such as triptans, ergots, calcitonin gene-related peptide (CGRP) receptor antagonists, and NSAIDs.	Zavegepant nasal spray provides an alternative route of administration for small molecule CGRP receptor antagonists compared to the current oral formulations. In general, additional options for acute treatment would be helpful to those who have contraindications

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		to currently available treatment options.
Benefit	• Two pivotal efficacy studies demonstrated efficacy of zavegepant for the acute treatment of migraine with or without aura. Both studies used the co-primary endpoints of pain freedom at 2 hours postdose and MBS at 2 hours postdose. Both studies demonstrated statistical significance of zavegepant 10 mg for both co-primary endpoints compared to placebo. Overall, 7-9% and 8-9% more zavegepant-treated patients experience pain freedom at 2 hours postdose and MBS freedom at 2 hours postdose, respectively, compared to placebo-treated patients. • In one of the pivotal trials, study 301, zavegepant 10 mg demonstrated statistical significance for the following key secondary endpoints: Pain relief at 2 hours, return to normal function at 2 hours, sustained pain freedom from 2 to 48 hours, freedom from photophobia at 2 hours, and freedom from phonophobia at 2 hours. These findings further support zavegepant efficacy demonstrated on the co-primary endpoints.	The efficacy of 10 mg zavegepant for the acute treatment of migraine with or without aura has been demonstrated in two adequate and well-controlled trials. Compared to placebo-treated patients, zavegepant treated patients are more likely to experience migraine pain freedom at 2 hours postdose and MBS freedom at 2 hours postdose.
Risk and Risk Management	• The theoretical safety issues of cardiovascular, cerebrovascular, peripheral vascular, gastrointestinal, hepatotoxicity, and local toxicity risk were evaluated. There were no clear safety signals identified. • In the double-blind, controlled, clinical trials, adverse events that occurred in at least 1% of zavegepant-treated patients were, taste disorder, nausea, nasal discomfort, vomiting, throat irritation, nasal congestion, and fatigue/somnolence. In the open-label study, adverse events that occurred in at least 3% of zavegepant-treated patients were taste disorder, nasal discomfort, COVID-19, nasal congestion,	Overall, the safety profile appears acceptable. There were a notable number of local irritative adverse events (AEs) that were common such as the taste disturbance. However, such incidence of these AEs is similar to other nasal sprays used for the treatment of migraines. Patients with major cardiovascular disease were not fully evaluated due to exclusion criteria.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	nausea, throat irritation, back pain, pyrexia, myalgia, rhinorrhea, arthralgia, abnormal liver function tests, abdominal pain/dyspepsia, oropharyngeal discomfort, and fatigue/somnolence. • Overall, the clinical trials included healthier and younger patients. In addition, patients with major cardiovascular disease were essentially excluded.	Enhance pharmacovigilance for myocardial infarction, stroke, and hepatotoxicity is recommended due to theoretical cardiovascular and cerebrovascular risk, and potential hepatoxicity risk.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

x	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		x	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Migraine is a common, chronic, neurologic disorder that can be a serious and potentially disabling condition affecting the patient's quality of life. The severity and frequency can vary,

with patients typically experiencing recurrent, moderate to severe headaches. In the United States, approximately 21% of women and 10.7% of men have migraine headaches (Burch 2018), and many of migraine patients report reduced work or school productivity. The prevalence of migraine is highest between the ages of 25 and 55 years, then decreases with age (Dodick, 2018). A migraine aura may occur prior to or at onset of headache and may occur in the absence of pain. Patients may have auras lasting minutes, of unilateral reversible visual, sensory, or other central nervous system symptoms one or two days prior to onset of the headache.

The International Headache Society (IHS) has established the International Classification for Headache Disorders, 3rd edition (ICHD-3) which include the diagnostic criteria for migraine with or without aura. Per the ICHD-3 definition, a migraine is a recurrent headache disorder presenting with episodes lasting 4-72 hours. The headaches should have two of the four characteristics of unilateral, pulsating, moderate or severe intensity, or aggravated by routine physical activity. In addition, the headache should have nausea and/or vomiting, or photophobia and phonophobia. Lastly, the symptoms are not better accounted for by another ICHD-3 diagnosis.

2.2. Analysis of Current Treatment Options

There are multiple FDA-approved and off-label therapies for the acute treatment of migraine. Options for prescription treatment of acute migraines include drugs such as triptans, ergots, CGRP receptor antagonists, non-steroidal anti-inflammatory drugs (NSAIDs). Non-prescription options include NSAIDs and acetaminophen/caffeine/aspirin combination. There were previous development programs for small molecule CGRP receptor antagonist that were discontinued due to hepatotoxicity concerns. Although ubrogepant, rimegepant, and atogepant were approved more recently with no clear indication of hepatotoxicity in their development programs, overall hepatotoxicity is still a safety signal of interest in small molecule CGRP receptor antagonist development programs.

Table 1 Summary of Acute Treatment for Migraine*

Product (s) Name	Year of Approval for Migraine	Route	Important Safety and Tolerability Issues	Other Comments (for example, subgroups addressed)
FDA Approved Treatments				
ERGOTS				
Dihydroergotamine (DHE) Nasal Spray 2 mg	1997	Intranasal	CYP3A4 inhibitor interaction; contraindicated with cardiovascular disease; fibrotic complications	
Dihydroergotamine (DHE) Nasal Spray 1.45 mg	2021	Intranasal	CYP3A4 inhibitor interaction;	

			contraindicated with cardiovascular disease; fibrotic complications	
DHE 1 mg injection	1946	Sub-cutaneous, Intravenous, and intramuscular	CYP3A4 inhibitor interaction; contraindicated with cardiovascular disease; fibrotic complications	
Ergotamine 2 mg	1982	Sublingual		
Ergotamine/caffeine (Oral 1mg/100mg, Rectal 2 mg/100mg)	1948	Oral and Rectal		
TRIPTANS				
Almotriptan 12.5 mg	2001	Oral Tablet	Contraindicated in patients with coronary artery disease, coronary artery vasospasm, conduction pathway disorders, cerebrovascular disease, hemiplegic or basilar migraine, peripheral vascular disease, ischemic bowel disease or uncontrolled hypertension; Warnings/precautions in patients with history of myocardial ischemia, arrhythmias, cerebral hemorrhage, subarachnoid hemorrhage, or stroke	Indicated for patients age 12 to 17 years old
Eletriptan 20, 40 mg	2002	Oral Tablet		Interacts with CYP3A4 inhibitors
Frovatriptan 2.5 mg	2001	Oral Tablet		
Naratriptan 1, 2.5 mg	1998	Oral Tablet		
Rizatriptan 5, 10 mg	1998	Oral Tablet		Indicated for patients age 6 to 17 years old
Sumatriptan Oral 25, 50, 100mg	1992	Oral Tablet		
Sumatriptan Nasal Spray 10, 20 mg		Intranasal		
Sumatriptan Nasal Powder 22 mg	2016	Intranasal		
Sumatriptan SC 4, 6 mg	2009	Sub-cutaneous		
Zolmitriptan NS 2.5, 5 mg	2015	Intranasal		Indicated for patients 12 years of age or older
Zolmitriptan ZMT 1.25, 2.5, 5 mg	2001	Oral Disintegrating tablet		
Zolmitriptan Oral 2.5, 5 mg	1997	Oral Tablet		
Sumatriptan/naproxen 85/500 mg (NSAID included)	2008	Oral Tablet		Indicated for patients 12 years and older; Cardiovascular risk, increased risk of bleeding due to naproxen component
NSAIDS				
Celecoxib oral solution (Elyxyb)	2020	Oral Solution	Cardiovascular risk for thrombotic events, myocardial infarction, and stroke; gastrointestinal adverse events, especially in elderly, dysgeusia	

Diclofenac (Cambia) 50 mg	2009	Oral (Packet)	Cardiovascular risk for thrombotic events, myocardial infarction, and stroke; gastrointestinal adverse events, especially in elderly	
5-HT1F receptor agonists				
Lasmiditan	2019	Oral	Driving impairment for up to 8 hours; May lower heart rate; Adverse events include dizziness, fatigue, paresthesia, sedation, nausea and/or vomiting, muscle weakness;	
CGRP antagonist				
Rimegepant 75 mg	2020	Oral	Nausea	Interacts with CYP3A4 Inhibitors/inducers; inhibitors of BCRP and P-gp efflux transporters
Ubrogepant 50 mg, 100 mg	2019	Oral	Nausea, somnolence, dry mouth	Interacts with CYP3A4 Inhibitors/inducers; substrate of BCRP and P-gp efflux transporters
Devices				
Cefaly ACUTE device	2017	Device	Contraindicated with recent trauma to skull/face or with skin conditions/rashes	
Cerena device	2013	Device	Contraindicated in patients with magnetic metals in head, neck or upper body, or pacemakers, or other implanted devices	
GammaCore device	2017	Device		
Nonprescription, FDA approved				
NSAIDs (ibuprofen)	2000 (Advil Migraine)	Oral Tablet, Capsule	Gastrointestinal toxicity, bleeding complications	Advil Migraine is a nonprescription drug indicated for the treatment of migraine.
Acetaminophen/aspirin/caffeine	1998 (Excedrin Migraine)	Tablet	Overuse, see effects for individual categories	Excedrin Migraine is a nonprescription drug indicated for the temporary relief of mild to moderate pain

				associated with migraine headache.

*Modified from Dr. Viveca Livezy's clinical review of NDA 212157.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Zavegepant is an NME and not currently marketed in the United States for any indication.

3.2. Summary of Presubmission/Submission Regulatory Activity

The investigational new drug (IND) application 134120 was opened for zavegepant on September 5, 2018, to conduct studies that were to evaluate zavegepant for the acute treatment of migraine. At that time, the applicant established that they planned to demonstrate efficacy and safety of zavegepant for the acute treatment of migraine. On November 3, 2018, a "May Proceed" letter was issued.

During the Pre-IND meeting, on August 1, 2017, the Division recommended a more conservative dose escalation of a factor of 2 times versus the planned (b) (4) for the Phase 1 single and multiple ascending dose study. In addition, the Division recommended that the applicant provide detailed information, in the opening IND submission, on how they plan to monitor for liver toxicity, given the hepatotoxicity seen in other products in the same class as zavegepant.

At the end-of-phase 2 (EOP2) meeting on March 16, 2020, the Division recommended that the applicant characterize the hepatic liability of the daily or near daily use of zavegepant by conducting a two to three-month study with 300 migraine patients or healthy volunteers using zavegepant on a near daily basis with a comparator arm. At that time, the safety database they proposed was inadequate to address the hepatic safety of the product with near daily use. The applicant responded that it believed intranasal acute treatment would limit how frequent patients would use a product regarding a daily or near daily dosing, therefore the applicant thought it would not be feasible. The applicant proposed using an oral formulation of zavegepant to evaluate for potential hepatotoxicity. The Division responded to the applicant: "Your proposal to conduct a dedicated hepatic safety study with an oral formulation of vazegepant [zavegepant] would be acceptable if, as you suggest, exposures with the oral product are at least what will be achieved with the intranasal formulation. Final agreement on the acceptability of such a study would be dependent upon the review of the full study protocol. Additionally, the results of that trial would be necessary to support your planned NDA submission."

The Division also stated that whether a planned concentration-QT (cQT) assessment of zavegepant in the single ascending dose (SAD) and multiple ascending dose (MAD) studies was adequate could not be determined until review of the QT assessment report and that the applicant should submit their QT assessment reports. The Division informed the applicant that use of endpoints (b) (4) at various time points is not recommended and that the applicant "should evaluate pain freedom at various time points, including sustained pain freedom at either 24 or 48 hours." In addition, the applicant was informed of the secondary endpoints that the Division would consider supportive of efficacy by referring the applicant to the Guidance for Industry, "Migraine: Developing Drugs for Acute Treatment". Lastly, the Division recommended analyzing secondary endpoints with a hierarchical approach, and that the secondary endpoints should be ordered based on their clinical meaningfulness. There was also an EOP2 meeting for chemistry, manufacturing, and controls (CMC) issues on May 29, 2020.

On February 5, 2021, the Division notified the applicant that they agreed with the Agreed iPSP submitted by the applicant. The original applicant, Biohaven Pharmaceutical Holding Company Ltd., became a subsidiary of Pfizer Incorporate. Therefore, the sponsorship for zavegepant-related INDs (134120 (b) (4)) and NDA 216386 was transferred to Pfizer Inc.

Summary of dates for regulatory interactions:
Pre-IND meeting: August 1, 2017
Initial IND: September 5, 2018
EOP2 meeting: March 16, 2020
NDA filing: March 9, 2022

3.3. Foreign Regulatory Actions and Marketing History

Zavegepant is currently not approved or marketed in any foreign country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI conducted inspections of four clinical sites. There were two sites inspected for study 201, and two sites inspected for study 301. In addition, there was an inspection of the contract research organization (CRO), (b) (4) to whom responsibilities of site monitoring, project management, and data management were transferred from the applicant Biohaven Pharmaceuticals, Inc., for study 301. OSI found that the studies had been conducted adequately and the data generated by these sited and submitted by the applicant appear acceptable in support of the respective indication. Please see the Clinical Inspection Summary

4.2. Product Quality

Please refer to the Chemistry, Manufacturing, and Controls review by the Office of Product Quality (OPQ) for further details.

4.3. Clinical Microbiology

N/A

4.4. Nonclinical Pharmacology/Toxicology

Please refer to the review by Dr. Elizabeth Khory, nonclinical reviewer.

4.5. Clinical Pharmacology

Please refer to the clinical pharmacology review. In the review, the review team noted that "the zavegepant exposures following 100 mg oral dose is comparable to that after 10 mg IN dosing (100 mg oral zavegepant: $Cmax_{ss}$, 9 ng/mL and AUC_{0-24}, 38 ng•h/mL ; 10 mg IN zavegepant: $Cmax_{ss}$, 13 ng/mL and AUC_{0-24}, 33 ng•h/mL)". This is relevant to the study that used 100 mg oral zavegepant to evaluate the hepatoxicity for this current application.

4.6. Devices and Companion Diagnostic Issues

Zavegepant 10 mg nasal spray is supplied in a disposable single use unit dose (to one nostril) nasal spray drug – device combination product, using (b) (4) spray device. The (b) (4) unit dose spray device is commonly used in many approved drug products. Please refer to the Chemistry, Manufacturing, and Controls review by the OPQ for further details.

4.7. Consumer Study Reviews

N/A

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2 Clinical Trials Relevant to NDA 216386

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration	No. of patients treated	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
BHV3500-201	Randomized, double-blind, placebo-controlled, dose-ranging study (pivotal efficacy)	5 mg, 10 mg, or 20 mg intranasal zavegepant	Co-Primary endpoints: Pain freedom at 2 hours post-dose MBS freedom at 2 hours post-dose	Single attack	Total N=1588 5 mg N=388 10 mg N=394 20 mg N=403 Placebo=403	History of 2-8 migraines/month; ≥18 years	82/1 (U.S)
BHV3500-301	Randomized, double-blind, placebo-controlled study(pivotal efficacy)	10 mg intranasal zavegepant	Co-Primary endpoints: Pain freedom at 2 hours post-dose MBS freedom at 2 hours post-dose	Single attack	Total N=1282 10 mg N=629 Placebo N=653	History of 2-8 migraines/month; ≥18 years	90/1 (U.S)
Studies to Support Safety							
BHV3500-106	Open-label, repeat daily dosing study	100 mg daily oral zavegepant	Safety/tolerability	8 weeks	Total N=364	Healthy adult subjects; ≥18 years	10/1 (U.S)
BHV3500-202	Long-term, open-label extension, repeat dosing study	10 mg intranasal zavegepant up to 8 times per month	Safety/tolerability	Up to 52 weeks	Total N=600	History of 2-8 migraines/month; ≥18 years	63/1 (U.S)

MBS=most bothersome symptom

5.2. Review Strategy

The applicant has proposed the 10 mg dose as the to-be-marketed dose. There are two pivotal studies that evaluated the 10 mg dose: one study is a dose-ranging study that included 5 mg, 10 mg, and 20 mg doses, and the other study evaluated only the 10 mg dose. This review will evaluate the data for the two pivotal studies to determine whether the 10 mg dose is approvable based on its efficacy profile. To determine whether the 10 mg dose is approvable will also be based on the safety profile of the 10 mg intranasal dose. For efficacy, studies BHV3500-201 and BHV3500-301 will be reviewed, which I will refer to as study 201 and 301 throughout this review. For safety, studies 201 and 301 will be reviewed along with the results of the open-label, repeat daily dosing, hepatotoxicity study (BHV3500-106) and the long-term, open-label, safety study (BHV3500-202). Studies BHV3500-106 and BHV3500-202 will be referred to as study 106 and 202 throughout this review.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study BHV3500-201: Phase II/III: Double-blind, Randomized, Placebo-Controlled, Dose-Ranging Trial of BHV-3500 for the Acute Treatment of Migraine

6.1.1. Study Design

Overview and Objective

The primary objective of study 201 was to evaluate the efficacy of zavegepant compared to placebo for the acute treatment of a single migraine attack by utilizing the co-primary endpoints of pain freedom and MBS freedom associated with migraine, both at 2 hours post-dose, and identify an optimal dose for the Phase 3 clinical trial.

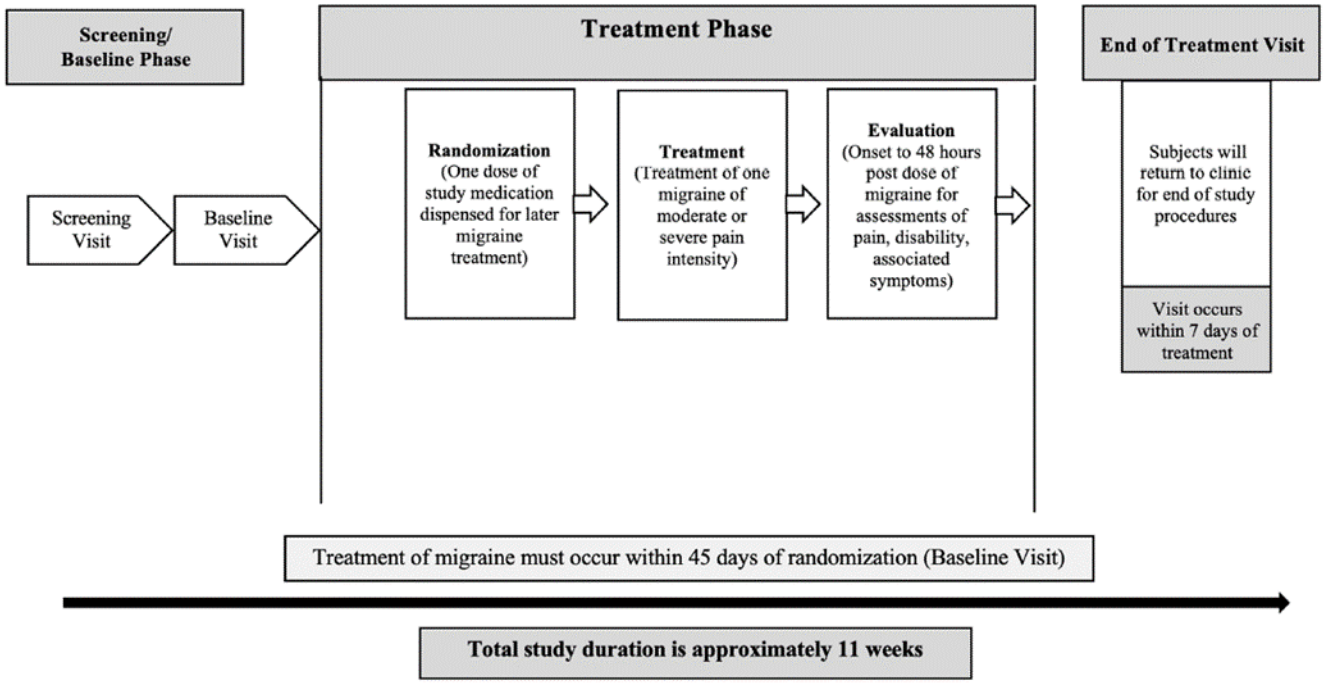
Trial Design

Basic Study Design

Study 201 was a Phase 2/3, double-blind, randomized, placebo-controlled, multicenter, outpatient study to evaluate the safety and efficacy of a single IN zavegepant dose versus placebo in the treatment of moderate or severe migraine. Patients were randomized, 1:1:1:1, to receive one Aptar UDS liquid spray device containing a single dose of one of three zavegepant dose levels (5 mg, 10 mg, or 20 mg) or placebo. The total duration of the study was approximately 11 weeks. The study included a screening phase (lasting 3 to 28 days) and a treatment phase (of up to 45 days or until a subject experienced a migraine attack of moderate or severe intensity), followed by an end of treatment (EOT) visit that occurred within 7 days of treatment (Figure 1). There was no option for a second dose. If a patient did not experience a

migraine headache of moderate or severe intensity within 45 days after randomization, they were still required to complete all end of treatment visit procedures.

Figure 1: Study 201 Design Schematic



Source: Clinical Overview, Figure 3

Diagnostic Criteria

The applicant used the diagnosis of migraine consistent with the ICHD-3 definition.

Key Inclusion Criteria

1. Male or female patients age ≥18 years and older
2. At least one-year history of migraine with or without aura
3. No more than 8 migraine attacks of moderate or severe intensity per month within last 3 months prior to the screening visit
4. Migraine onset prior to age 50
5. Less than 15 days with headaches per month in each of the 3 months prior to screening

Key Exclusion Criteria

1. Hemiplegic or basilar migraine
2. History of HIV, hepatitis B or C
3. History of uncontrolled, unstable, or recently diagnosed cardiovascular disease including ischemic heart disease, coronary artery vasospasm, cerebral ischemia. Patients with a

history of myocardial infarction, acute coronary syndrome, percutaneous coronary intervention, cardiac surgery, stroke, or transient ischemic attack during the 6 months prior to screening.

4. Uncontrolled hypertension or diabetes.
5. Diagnosis of major depression, pain syndromes, psychiatric conditions, dementia, or significant neurological disorders.
6. History of gastric or small intestinal surgery or has a disease that causes malabsorption
7. History of alcohol or drug abuse.
8. Acute or chronic treatment with over-the-counter (OTC) or prescription nasal sprays.
9. History of nasal surgery in prior 6 months.
10. Evidence at screening of significant nasal conditions that may affect the administration or absorption.
11. Body mass index (BMI) ≥35 kg/m^2
12. History of Gilbert's Syndrome or any other active hepatic or biliary disorder.
13. Female patients who are pregnant, lactating, breastfeeding, or unwilling or unable to use acceptable contraceptive method.
14. Estimated glomerular filtration rate (GFR) of ≤ 40 $ml/min/1.73m^2$.
15. ECG findings including left or right bundle branch block, intraventricular conduction defect; QT interval > 470 msec; QRS≥150 msec.
16. Serum bilirubin >1 x ULN; neutrophil count ≤1000/uL; AST or ALT > 1xULN, HbA1c > 7%.

Dose Selection

Using data from a nonclinical study and a Phase 1, single ascending dose PK study, it was predicted that an effective human IN dose would be in a range of 2 mg to 20 mg. There was also tolerability across this range. Therefore, given the tolerability of zavegepant across a wide dose range, the trial evaluated the efficacy and dose-response of zavegepant across the dose range (5, 10, and 20 mg) in patients with a migraine attack.

Study Treatments/Blinding

This was a double-blind placebo-controlled trial with 5 mg IN zavegepant, 10 mg IN zavegepant, 20 mg IN zavegepant, or matching placebo.

Assignment to Treatment

Randomization and treatment assignment occurred through the interactive web response system (IWRS). All eligible patients who met study entry criteria were randomized across four treatment groups, in a 1:1:1:1 ratio to either 5 mg IN zavegepant, 10 mg IN zavegepant, 20 mg IN zavegepant, or matching placebo. The randomization was stratified by current use of preventive medications (yes/no).

Dose Modification/Dose Discontinuation

The dose of the investigational product (IP) was fixed and could not be adjusted.

Procedures and Schedule

The schedule of study procedures and assessments is summarized in Table 3. I have modified the table from the applicant's materials to only include key assessments.

Table 3 Schedule of Procedures and Assessments for Study 201

Procedure	Screening	Baseline/ Randomization Visit (Day 1)	Onset of moderate or severe migraine	Post Study Medication Administration: 15, 30, 45, 60 and 90 minutes 2, 3, 4, 6, 8, 24 and 48 hours	End of Treatment Visit
Physical Examination, ECG, Laboratory Testing, Urinalysis	X				X
Nasal Inspection	X	X			X
Vital Signs, Physical Measurements, Sheehan Suicidality Tracking Scale (S-STS)	X	X			X
Adverse Event and Serious Adverse Event Assessment	X	X	X	X	X
Pregnancy Test	X (Serum)	X (Urine)	X (Urine)		X (Serum)
Urine drug screen for drugs of abuse	X				X

Source: Study 201 Protocol version 4.0, Table 1

Dietary Restrictions/Instructions

N/A

Concurrent medications

The below medications are prohibited prior to randomization and during the course of this study or as specified.

1. St. John's Wort, butterbur root or extracts, modafinil (PROVIGIL®), barbiturate-containing products and marijuana.
2. Barbiturate-containing products (e.g., Fioricet, Fiorinal, butalbital, phenobarbital) should not be taken 14 days prior to randomization and throughout the study.
3. History of use of ergotamine medications on ≥10 days/month for ≥3 month
4. History of non-narcotic analgesic intake on ≥15 days per month for ≥3 month (e.g., acetaminophen, NSAIDs, gabapentin etc.) for other pain indications
5. Use of narcotic medication, such as morphine, codeine, oxycodone and hydrocodone.
6. Use of all acetaminophen or acetaminophen containing products at daily dosing levels
7. Muscle relaxants (baclofen is allowed as rescue medication).
8. Use of strong CYP3A4 inhibitors and inducers with BHV-3500 is prohibited during the study.
9. OTC or prescription topical nasal steroids, oxymetazoline, topical nasal antihistamines, topical nasal anticholinergics, and topical nasal mast cell stabilizers should not be taken within 14 days prior to the screening visit and throughout the study.
10. Prophylactic migraine medications are permitted to remain on therapy provided they have been on a stable dose for at least 3 months prior to study entry.
11. Use of CGRP antagonists.

Treatment Compliance

Accountability and compliance verification was documented. Subjects were counseled on the importance of taking the study drug as directed. Patients were to return for their end-of-treatment visit within 45 days of baseline visit if they did not have a qualifying migraine attack or take their study medication and return, their study medication.

Rescue Medication

Other headache medications were prohibited during the first 2 hours postdose of study drug administration. If a patient did not experience migraine relief at 2 hours postdose, the patient was permitted to use only the following rescue medications: aspirin; ibuprofen; acetaminophen, up to 1,000 mg/day (this includes Excedrin® Migraine); Naprosyn (or any other type of NSAID); antiemetics (e.g., metoclopramide or promethazine); or baclofen.

If the migraine was relieved by study drug at 2 hours postdose but returned to a moderate or severe intensity level between 2 and 48 hours later, subjects were permitted to take the same rescue therapy as outlined above.

If after 48 hours postdose of study drug (and before returning to the clinical site for the EOT visit), patients were allowed to take their prescribed standard of care medications for

Subject Completion/Discontinuation/Withdrawal

Patients could withdrawal for any reason. All patients who discontinued were to comply with protocol specified end of treatment procedures.

Study Endpoints

Co-Primary Endpoints

1. Pain freedom at 2 hours postdose.
2. Freedom from the most bothersome symptom (MBS), associated with migraine, at 2 hours postdose.

Secondary Endpoints

1. Pain relief at 2 hours postdose
2. Return to normal function at 2 hours postdose according to the FDS
3. Probability of requiring rescue medication within 24 hours of initial treatment
4. Freedom from photophobia at 2 hours postdose
5. Freedom from phonophobia at 2 hours postdose
6. Pain relief at 60 minutes postdose
7. Patient's ability to function normally at 60 minutes postdose according to the FDS
8. Pain relief at 30 minutes postdose
9. Patient's ability to function normally at 30 minutes postdose according to the FDS
10. Sustained pain relief from 2 to 24 hours postdose
11. Sustained pain freedom from 2 to 24 hours postdose
12. Sustained pain relief from 2 to 48 hours postdose
13. Sustained pain freedom from 2 to 48 hours postdose
14. Freedom from nausea at 2 hours postdose
15. Pain relapse from 2 to 48 hours postdose

Definitions

Pain Freedom: Defined as having a pain level of none at a single time point post-dose.

Pain Relief: Defined as a pain level of none or mild at a single time point post-dose.

Sustained Pain Freedom: Defined as pain freedom with no intervening of rescue medication, and pain level of none at all described time points.

Sustained Pain Relief: Defined as pain relief with no intervening of rescue medication, and pain level of none or mild at all described time points.

Statistical Analysis Plan

Analysis Populations

1. Enrolled: Patients who signed an informed consent form (ICF) and were assigned a subject identification number
2. Randomized: Enrolled patients who received a randomization treatment assignment from the IWRS
3. Treated: Enrolled patients who took study therapy
4. Modified intent-to-treat (mITT): Treated patients who were randomized only once, had moderate to severe pain at on-study migraine attack onset, and had any non-missing, postbaseline efficacy data

The mITT population for the secondary endpoints of photophobia, phonophobia, and nausea freedom at 2 hours, are patients who reported that symptom at migraine onset. For the secondary endpoints evaluating a return to normal function, the mITT population included patients who had functional disability at on-study migraine attack onset.

Sample Size Estimation

The sample size was determined based on if 95% of the 400 subjects randomized to each treatment group treated a migraine attack on-study, there would be roughly 380 mITT subjects in each treatment group. The applicant determined that if the true response rates for pain freedom at 2 hours were 22% and 12% in the zavegepant and placebo groups of the study, respectively, then a chi-square test at alpha = 0.0167 would have 90% power. Furthermore, if the true response rates for MBS freedom at 2 hours were 45% and 32% in the zavegepant and placebo groups, respectively, then a chi-square test, at alpha = 0.0167, would have 90% power. Assuming that the endpoints were independent, the power for both endpoints jointly was approximately 80%.

Hypothesis Testing

Type I error in this study was controlled by a hierarchical gate-keeping procedure. First, the two co-primary endpoints were tested. Each zavegepant dose group was tested for superiority against placebo at a Bonferroni corrected alpha = 0.0167 level for both co-primary endpoints. If both coprimary endpoint tests were significant for a zavegepant dose group versus placebo, then the secondary endpoints were tested for that zavegepant dose group versus placebo using a hierarchical gate-keeping procedure, with each test in the hierarchy conducted at alpha = 0.0167.

If a test in the hierarchy was not significant, then any further tests on endpoints in the sequence would have p-values presented only for descriptive purposes, and no conclusions would be drawn from those results.

Pre-Specified Methods for Handling Missing Data

Subjects with missing data at a single time point were classified as failures. This missing data imputation method was applied to endpoints based on data from a single time point. For the co-primary endpoints, a patient with missing data was considered a treatment failure.

Patients taking rescue medication at or before the 2-hour postdose time point are imputed as failures.

Protocol Amendments

There were four versions of the protocol, with the original protocol issued on January 30, 2019, per the applicant. The second version of the protocol was submitted to the Agency on February 25, 2019. This version added a check for rescue medication and concomitant medication paper diary to be completed at onset of migraine and post study medication time points. In addition, the arrangement of the secondary objectives and endpoints was completed, and the number of doses being tested were clarified. In the third version of the protocol, submitted on May 15, 2019. Changes in the third version included addition of an otoscope as a permitted tool for nasal inspection, added Gilbert's syndrome to the exclusion criteria, removed indirect bilirubin as an exclusion criterion, and clarified the hypertension exclusion criteria. Protocol version 4 was submitted on September 12, 2019, which corrected the schedule of assessment to include the Functional Disability Scale (FDS) at the onset of migraine, and at the same time points as the headache severity ratings.

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant states that the study was conducted in compliance with the protocol, Good Clinical Practice (GCP) guidelines, and all applicable regulations, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations (title 21), any IRB/IEC requirements relative to clinical studies.

Financial Disclosure

Patient Disposition

Enrolled: 2154
Randomized: 1673 (placebo: 420, 5 mg: 418, 10 mg: 417, 20 mg: 418)
Treated (Received at least 1 dose of double-blind study drug): 1588 (placebo: 403, 5 mg: 388, 10 mg: 394, 20 mg: 403)
mITT population (Treated subjects who were randomized only once, had moderate to severe pain at on-study migraine attack onset, and had any non-missing, postbaseline efficacy data): 1581 (placebo: 401, 5 mg: 387, 10 mg: 391, 20 mg: 402)

Of the randomized patients, 1581 patients (94.5%) were included in the mITT. Eight-five patients were randomized but not treated, and seven patients were treated but were not in the mITT. Of those seven patients, all were excluded from the mITT population because they did not have post-baseline efficacy data.

Protocol Violations/Deviations

Significant protocol deviations were any deviations that could affect safety of patients or the integrity of the study. The three most common protocol deviations were electronic clinical outcome assessment (eCOA) handheld diary noncompliance, concomitant medication, and noncompliance.

Table 4 Protocol Deviation or Violations in Randomized Patients for Study 201

Protocol Deviation	Placebo N=420 n(%)	5 mg Zavegepant N=418 n(%)	10 mg Zavegepant N=417 n(%)	20 mg Zavegepant N=418 n(%)
eCOA Handheld Diary Noncompliance	51 (12.1)	41 (9.8)	55 (13.2)	63 (15.1)
Concomitant Medications	35 (8.3)	35 (8.4)	43 (10.3)	48 (11.5)
Noncompliance	22 (5.2)	31 (7.4)	29 (7.0)	30 (7.2)
Drug Administration	18 (4.3)	22 (5.3)	22 (5.3)	22 (5.3)
Informed Consent	7 (1.7)	7 (1.7)	12 (2.9)	12 (2.9)
Stratification	8 (1.9)	3 (0.7)	5 (1.2)	7 (1.7)
Regulatory	5 (1.2)	3 (0.7)	0	5 (1.2)
Exclusion Criteria	8 (1.9)	2 (0.5)	1 (0.2)	0
Visit Schedule	0	1 (0.2)	1 (0.2)	0
Inclusion Criteria	1 (0.2)	0	0	0

Source: Study 201 case study report (CSR), Table 9-4

Reviewer comment: The protocol deviations appear to be generally balanced. There is a noted difference between the placebo, 5 mg, and 20 mg groups in regard to eCOA handheld diary noncompliance and concomitant medications deviations.

Table of Demographic Characteristics

No significant baseline imbalances in the demographic characteristics were noted between placebo and treatment groups in the mITT population (Table 5).

Table 5 Study 201 Demographic Characteristics of the mITT Population

Demographic Parameters	Placebo (N=401) n (%)	5 mg (N=387) n(%)	10 mg (N=391) n(%)	20 mg (N=402) n(%)
Sex				
Male	63 (15.7)	51 (13.2)	58 (14.8)	58 (14.4)
Female	338 (84.3)	336 (86.8)	333 (85.2)	344 (85.6)
Age				
Mean years (SD)	39.9 (12.00)	41.9 (12.59)	41.4 (12.94)	40.0 (12.96)
Median (years)	39.0	40.0	40	39
Min, max (years)	18, 79	18, 70	18, 74	18, 74
Age Group*				
18 to 40	203 (50.6)	181 (46.8)	186 (47.6)	208 (51.7)
41 to 64	190 (47.4)	188 (48.6)	185 (47.3)	178 (44.3)
65+	8 (2.0)	18 (4.7)	20 (5.1)	16 (4.0)
Race				
White	328 (81.8)	299 (77.3)	296 (75.7)	315 (78.4)
Black or African American	58 (14.5)	65 (16.8)	72 (18.4)	62 (15.4)
Asian	13 (3.2)	17 (4.4)	13 (3.3)	15 (3.7)
American Indian or Alaska Native	1 (0.2)	2 (0.5)	0	3 (0.7)
Native Hawaiian/ Pacific Islander	0	0	1 (0.3)	0
Other/Multiple	1 (0.2)	4 (1.0)	9 (2.3)	7 (1.7)
Ethnicity				
Hispanic or Latino	81 (20.2)	64 (16.5)	69 (17.6)	72 (17.9)
Not Hispanic or Latino	320 (79.8)	323 (83.5)	322 (82.4)	330 (82.1)
Concomitant preventive medication				
Yes	54 (13.5)	54 (14.0)	50 (12.8)	57 (14.2)
Body Mass Index (BMI) kg/m²				
Mean (SD)	27.54 (4.542)	27.40 (4.794)	27.35 (4.486)	27.30 (4.495)
Median	27.5	27.8	27.5	27.3

Min, Max	17.7, 35.3	17.5, 35.0	16.6, 35.4	17.2, 34.9

Source: Study 201 CSR, Table 10-5

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

No significant imbalances in the migraine history characteristics for the mITT population were noted between placebo and treatment groups (Table 6).

Table 6 Study 201: Migraine History for the mITT Population

	Placebo (N=401)	5 mg (N=387)	10 mg (N=391)	20 mg (N=402)
Number of moderate to severe migraines per month by history				
Mean (SD)	5.0 (1.81)	4.9 (1.73)	4.9 (1.73)	4.9 (1.73)
Median	5.0	5.0	5.0	5.0
Min, Max	2, 8	2, 8	2, 8	2, 8
Most bothersome symptom (MBS)				
Nausea n(%)	96 (23.9)	90 (23.3)	99 (25.3)	98 (24.4)
Phonophobia n(%)	64 (16.0)	66 (17.1)	58 (14.8)	70 (17.4)
Photophobia n(%)	241 (60.1)	231 (59.7)	234 (59.8)	234 (58.2)
Primary migraine type				
Without aura n(%)	283 (70.6)	297 (76.7)	282 (72.1)	289 (71.9)
With aura n(%)	118 (29.4)	90 (23.3)	109 (27.9)	113 (28.1)

Source: Study 201 CSR, Table 14.1.5A

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Patients were instructed to return the study medication if they did not experience a moderate to severe migraine or did not take the study drug within 45 days of baseline visit

Overall, 14.2% of patients in the zavegepant group (14.4% in the 5 mg group, 13.2% in the 10 mg group, and 14.9% in the 20 mg group) and 12.4% in the placebo group took concomitant preventive medications for migraine. The most common were topiramate and non-selective monoamine reuptake inhibitors.

Rescue medication, after study drug administration and during the study, in the mITT population was taken similarly between the 5 mg zavegepant (29.7%), 10 mg zavegepant (29.9%), and placebo group (30.7%). The 20 mg zavegepant group had a smaller percentage of patients (24.4%) who used a rescue medication.

The co-primary endpoints for study 201 were:

1. Pain freedom at 2 hours postdose.
2. Freedom from the MBS associated with migraine at 2 hours postdose

The co-primary endpoints were evaluated for efficacy by comparing zavegepant-treated patients versus placebo-treated patients. The mITT population was used for the efficacy analyses. The 10 mg and 20 mg doses of zavegepant demonstrated statistically significant results for both co-primary efficacy endpoints compared to placebo, while the 5 mg dose of zavegepant did not demonstrate a statistically significant results for both co-primary endpoints (Table 7). Statistical reviewer, Dr. Yi Le, has verified these results and has confirmed the applicant's analysis and calculation of the co-primary efficacy endpoints.

Table 7 Study 201: Results of Co-Primary Efficacy Endpoints – mITT Patients

	Placebo (N = 401)	5 mg (N = 387)	10 mg (N = 391)	20 mg (N = 402)
Pain Freedom at 2 hours postdose				
n (%)	62 (15.5)	76 (19.6)	88 (22.5)	93 (23.1)
Percentage Difference (Zavegepant – Placebo)[a]	N/A	4.2	7.0	7.7
(98.3% CI)	N/A	(-2.3, 10.7)	(0.4, 13.7)	(1.1, 14.3)
p-value	N/A	0.1214	0.0113*	0.0055*
MBS freedom at 2 hours postdose				
n (%)	135 (33.7)	151 (39.0)	164 (41.9)	171 (42.5)
Percentage Difference (Zavegepant – Placebo)[a]	N/A	5.4	8.3	8.9
(98.3% CI)	N/A	(-2.8, 13.6)	(0.1, 16.5)	(0.7, 17.0)
p-value	N/A	0.1162	0.0155*	0.0094*

Source: Study 201 CSR, Table 10-1
[a] Stratified by prophylactic migraine medication use at randomization with CMH weighting
* Statistically significant

Data Quality and Integrity

No quality data issues were identified during the review of study 201. The data and analysis quality were adequate, and the statistical reviewer performed an independent review using the applicant's datasets. Please see Dr. Yi Le's statistical review.

The secondary efficacy endpoints were tested hierarchically in the following order:

1. Pain relief at 2 hours postdose
2. Return to normal function at 2 hours postdose according to the FDS
3. Probability of requiring rescue medication within 24 hours of initial treatment
4. Freedom from photophobia at 2 hours postdose
5. Freedom from phonophobia at 2 hours postdose
6. Pain relief at 60 minutes postdose
7. Patient's ability to function normally at 60 minutes postdose according to the FDS
8. Pain relief at 30 minutes postdose
9. Patient's ability to function normally at 30 minutes postdose according to the FDS
10. Sustained pain relief from 2 to 24 hours postdose
11. Sustained pain freedom from 2 to 24 hours postdose
12. Sustained pain relief from 2 to 48 hours postdose
13. Sustained pain freedom from 2 to 48 hours postdose
14. Freedom from nausea at 2 hours postdose
15. Pain relapse from 2 to 48 hours postdose

Zavegepant did not demonstrate statistically significant findings for the first secondary efficacy endpoint of pain relief at 2 hours postdose (Table 8 and 9). Therefore, due to hierarchical testing procedure, all of the following secondary efficacy endpoints were not statistically significant. For the 10 mg and 20 mg zavegepant dose groups the secondary endpoints of pain relief at 2 hours postdose and return to normal function at 2 hours postdose according to the FDS were nominally significant. For the 5 mg and 10 mg dose groups sustained pain relief from 2 to 48 hours postdose and pain relapse from 2 to 48 hours postdose were nominally significant. Sustained pain relief from 2 to 24 hours postdose, sustained pain freedom from 2 to 24 hours postdose, and sustained pain freedom from 2 to 48 hours postdose were nominally significant for all three zavegepant doses. The 20 mg dose was nominally significant for the secondary endpoints of probability of requiring rescue medication within 24 hours of initial treatment, freedom from photophobia at 2 hours postdose, and pain relief at 60 minutes postdose.

Table 8 Study 201 Results of Secondary Efficacy Endpoints

	Placebo (N = 401)	5 mg (N = 387)	10 mg (N = 391)	20 mg (N = 402)
(1) Pain relief at 2 hours postdose				
n/N (%)	215/401 (53.6)	224/387 (57.9)	237/391 (60.6)	246/402 (61.2)

Percentage Difference (Zavegepant – Placebo) [a]	N/A	4.2	7.1	7.5
(98.3% CI)	N/A	(-4.2, 12.7)	(-1.3, 15.4)	(-0.8, 15.9)
p-value	N/A	0.2296	0.0439*	0.0302*
(2) Return to normal function at 2 hours postdose				
n/N (%)	101/369 (27.4)	115/363 (31.7)	122/354 (34.5)	129/372 (34.7)
Percentage difference (Zavegepant – Placebo) [a]	N/A	4.3	7.1	7.3
(98.3% CI)	N/A	(-3.8, 12.3)	(-1.1, 15.3)	(-0.8, 15.4)
p-value	N/A	0.2039	0.0389*	0.0305*
(3) Probability of requiring rescue medication within 24 hours of initial treatment				
n/N (%)	109/400 (27.3)	96/385 (24.9)	101/388 (26.0)	80/397 (20.2)
Percentage difference (Zavegepant – Placebo) [a]	N/A	-2.4	-1.1	-7.1
(98.3% CI)	N/A	(-9.8, 5.1)	(-8.7, 6.4)	(-14.3, 0.0)
p-value	N/A	0.4502	0.7154	0.0172*
(4) Photophobia freedom at 2 hours postdose				
n/N (%)	109/358 (30.4)	118/337 (35.0)	121/340 (35.6)	134/354 (37.9)
Percentage difference (Zavegepant – Placebo) [a]	N/A	4.6	5.1	7.4
(98.3% CI)	N/A	(-3.9, 13.1)	(-3.4, 13.6)	(-1.0, 15.9)
p-value	N/A	0.1986	0.1494	0.0352*
(5) Phonophobia freedom at 2 hours postdose				
n/N (%)	94/276 (34.1)	115/260 (44.2)	107/239 (44.8)	114/263 (43.3)
Percentage difference (Zavegepant – Placebo) [a]	N/A	10.1	10.8	9.3
(98.3% CI)	N/A	(0.1, 20.1)	(0.6, 21.1)	(-0.6, 19.3)
p-value	N/A	0.0161*	0.0115*	0.0249*
(6) Pain relief at 60 minutes postdose				

n/N (%)	168/401 (41.9)	182/387 (47.0)	180/391 (46.0)	200/402 (49.8)
Percentage difference (Zavegepant – Placebo) [a]	N/A	5.1	4.2	7.8
(98.3% CI)	N/A	(-3.4, 13.5)	(-4.2, 12.6)	(-0.6, 16.2)
p-value	N/A	0.1495	0.2274	0.0259*
(7) Return to normal function at 60 minutes postdose				
n/N (%)	63/369 (17.1)	82/363 (22.6)	67/354 (18.9)	70/372 (18.8)
Percentage difference (Zavegepant – Placebo) [a]	N/A	5.5	1.8	1.7
(98.3% CI)	N/A	(-1.6, 12.5)	(-5.0, 8.7)	(-5.1, 8.4)
p-value	N/A	0.0624	0.5222	0.5517
(8) Pain relief at 30 minutes postdose				
n/N (%)	99/401 (24.7)	103/387 (26.6)	117/391 (29.9)	107/402 (26.6)
Percentage difference (Zavegepant – Placebo) [a]	N/A	1.9	5.3	1.9
(98.3% CI)	N/A	(-5.5, 9.4)	(-2.3, 12.8)	(-5.5, 9.3)
p-value	N/A	0.5359	0.0953	0.5398
(9) Return to normal function at 30 minutes postdose				
n/N (%)	20/369 (5.4)	32/363 (8.8)	27/354 (7.6)	37/372 (9.9)
Percentage difference (Zavegepant – Placebo) [a]	N/A	3.4	2.1	4.5
(98.3% CI)	N/A	(-1.2, 7.9)	(-2.3, 6.6)	(-0.2, 9.1)
p-value	N/A	0.0753	0.2445	0.0216
(10) Sustained pain relief from 2 to 24 hours postdose				
n/N (%)	143/401 (35.7)	169/387 (43.7)	166/391 (42.5)	179/402 (44.5)
Percentage difference (Zavegepant – Placebo) [a]	N/A	8	6.8	8.9
(98.3% CI)	N/A	(-0.3, 16.4)	(-1.5, 15.1)	(0.7, 17.1)
p-value	N/A	0.0205*	0.0495*	0.0098*
(11) Sustained pain freedom from 2 to 24 hours postdose				

n/N (%)	36/401 (9.0)	55/387 (14.2)	59/391 (15.1)	63/402 (15.7)
Percentage difference (Zavegepant – Placebo) [a]	N/A	5.3	6.1	6.7
(98.3% CI)	N/A	(-0.2, 10.7)	(0.6, 11.6)	(1.2, 12.2)
p-value	N/A	0.021*	0.0081*	0.0036*
(12) Sustained pain relief from 2 to 48 hours postdose				
n/N (%)	131/401 (32.7)	155/387 (40.1)	155/391 (39.6)	156/402 (38.8)
Percentage difference (Zavegepant – Placebo) [a]	N/A	7.4	7	6.2
(98.3% CI)	N/A	(-0.8, 15.6)	(-1.2, 15.1)	(-1.9, 14.2)
p-value	N/A	0.0297*	0.0404*	0.0676
(13) Sustained pain freedom from 2 to 48 hours postdose				
n/N (%)	30/401 (7.5)	50/387 (12.9)	54/391 (13.8)	53/402 (13.2)
Percentage difference (Zavegepant – Placebo) [a]	N/A	5.5	6.3	5.7
(98.3% CI)	N/A	(0.3, 10.6)	(1.1, 11.6)	(0.6, 10.8)
p-value	N/A	0.0111*	0.0038*	0.0075*
(14) Nausea freedom at 2 hours postdose				
n/N (%)	122/239 (51.0)	126/237 (53.2)	131/243 (53.9)	145/265 (54.7)
Percentage difference (Zavegepant – Placebo) [a]	N/A	1.8	2.9	3.7
(98.3% CI)	N/A	(-9.2, 12.7)	(-8.0, 13.7)	(-7.0, 14.3)
p-value	N/A	0.6987	0.5279	0.4092
(15) Pain relapse from 2 to 48 hours postdose				
n/N (%)	31/62 (50.0)	24/76 (31.6)	29/88 (33.0)	35/93 (37.6)
Percentage difference (Zavegepant – Placebo)[a]	N/A	-18.9	-17	-12.5
(98.3% CI)	N/A	(-38.6, 0.9)	(-36.4, 2.5)	(-31.9, 7.0)
p-value	N/A	0.0221*	0.0366*	0.1242

Source: Study 201 CSR, Table 10-5
[a] Stratified by prophylactic migraine medication use at randomization with CMH weighting

Table 9 Study 201: Secondary Endpoints Reaching Nominal Significance

	5 mg	10 mg	20 mg
Pain relief at 2 hours postdose		x	x
Return to normal function at 2 hours postdose according to the FDS		x	x
Probability of requiring rescue medication within 24 hours of initial treatment			x
Freedom from photophobia at 2 hours postdose			x
Freedom from phonophobia at 2 hours postdose	x	x	
Pain relief at 60 minutes postdose			x
Patient's ability to function normally at 60 minutes postdose according to the FDS			
Pain relief at 30 minutes postdose			
Patient's ability to function normally at 30 minutes postdose according to the FDS			
Sustained pain relief from 2 to 24 hours postdose	x	x	x
Sustained pain freedom from 2 to 24 hours postdose	x	x	x
Sustained pain relief from 2 to 48 hours postdose	x	x	
Sustained pain freedom from 2 to 48 hours postdose	x	x	x
Freedom from nausea at 2 hours postdose			
Pain relapse from 2 to 48 hours postdose	x	x	

x=nominal significance

Reviewer comment: Given the hierarchical testing procedure and the lack of statistical significance for the first secondary endpoint of pain relief at 2 hours postdose, all following tested secondary endpoints were not statistically significant. Therefore, I would recommend to not describe the nominally significant secondary endpoint for study 201 in the prescribing information (PI).

When looking at the 10 mg and 20 mg dose in relation to secondary endpoints, both doses had eight secondary endpoints that were nominally significant. The 10 mg dose had four nominally significant secondary endpoints that could be considered for labeling if they are statistically significant instead of nominally significant. There is no clear trend of greater efficacy for the 20 mg dose over the 10 mg dose, which would support marketing the 10 mg to minimize systemic exposure while providing efficacy.

There is a dose response for the co-primary endpoints when comparing the 5 mg to either the 10 mg or 20 mg zavegepant doses. The 5 mg dose did not demonstrate statistical significance, while the 10 and 20 mg doses did demonstrate statistical significance. When comparing the 10 mg to 20 mg dose, although there is a slightly higher percentage of responders for both co-primary endpoints, the response rate appear to be similar (Table 7).

Reviewer comment: The difference between the percentage of responders for 10 mg and 20 mg is small for both co-primary endpoints. Therefore, I agree with the applicant's selection of 10 mg to use in study 301 based on study 201 and the selection for the recommended dosing of zavegepant.

Sensitivity Analyses

The applicant performed the several sensitivity analyses. One sensitivity analysis was a "complete case" sensitivity analysis. In the "complete case" sensitivity analysis, patients who had missing data at the two-hour postdose time point were excluded (Table 10).

Table 10 Study 201: "Complete Case" Sensitivity Analysis

	Placebo (N = 401)	5 mg (N = 387)	10 mg (N = 391)	20 mg (N = 402)
Pain freedom at 2 hours postdose				
n/N (%)	62/390 (15.9)	76/377 (20.2)	88/379 (23.2)	93/387 (24.0)
Percentage difference (BHV-3500 - Placebo)		4.3	7.3	8.1
(98.3% CI)		(-2.0, 10.9)	(0.5, 14.1)	(1.3, 15.0)
P-value		0.1245	0.0103	0.0043
MBS freedom at 2 hours postdose				
n/N (%)	135/392 (34.4)	151/377 (40.1)	164/379 (43.3)	171/387 (44.2)
Percentage difference (BHV-3500 - Placebo)		5.6	8.9	9.7
(98.3% CI)		(-2.7, 13.9)	(0.5, 17.2)	(1.4, 18.1)
P-value		0.1068	0.0113	0.0051

Source: Study 201 CSR, Tables 14.2.1.1E and 14.2.1.2E

Reviewer comment: This sensitivity analysis performed by the applicant supports the results of the primary endpoint analysis for both co-primary endpoints.

6.2. Study BHV3500-301: Double-Blind, Randomized, Placebo-controlled, Safety and Efficacy Trial of BHV-3500 (Zavegepant) Intranasal for the Acute Treatment of Migraine

6.2.1. Study Design

Overview and Objective
The primary objectives of study 301 were to evaluate the efficacy of zavegepant compared to placebo for the acute treatment of a single migraine attack by utilizing the coprimary endpoints of pain freedom and freedom from the most bothersome symptom (MBS) associated with migraine, at 2 hours post-dose.

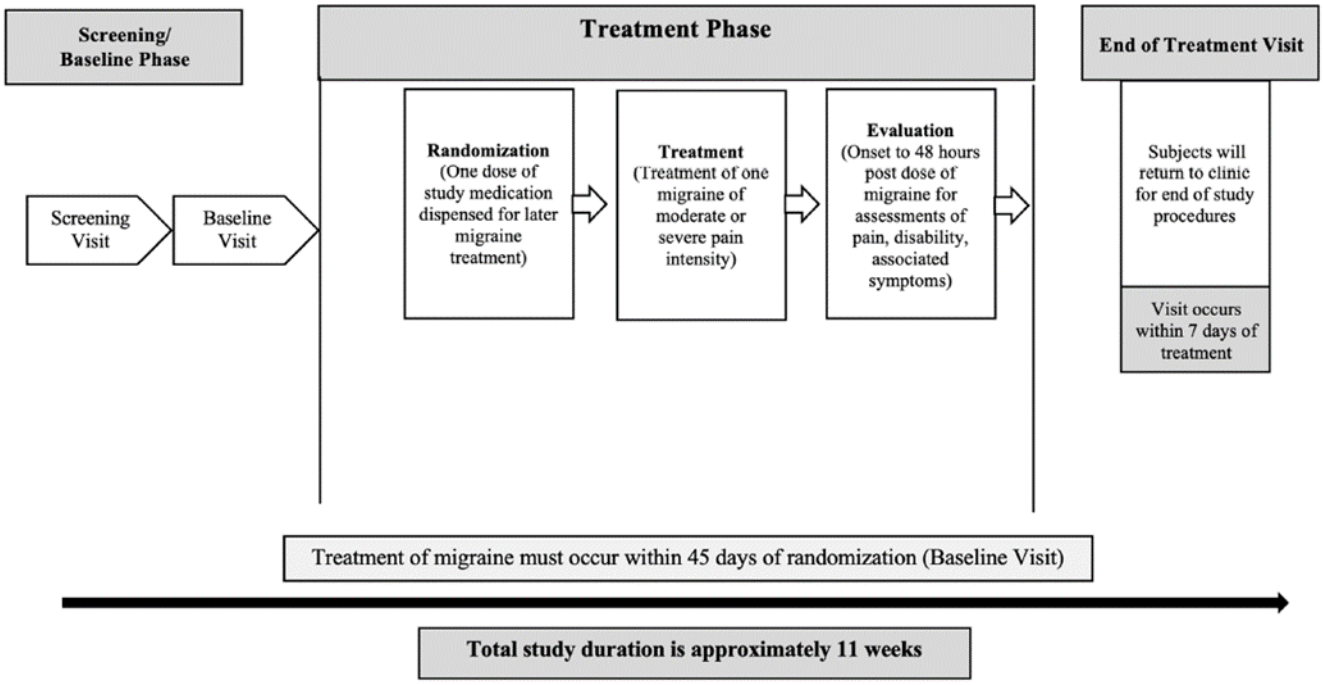
Study 301 was similar in design to study 201. However, there were notable differences between study 301 and 201. Unlike study 201, study 301 had one dose of zavegepant 10 mg compared to placebo and randomized 1:1. Therefore the statistical analysis plan differed to take in account this aspect. Also, within the statistical analysis plan the mITT population in Study 201 was defined similarly to the efficacy analysis set in study 301.

Another difference were the secondary endpoints. Study 301 included the same endpoints as study 201 but had two additional secondary endpoints of pain relief at 15 minutes postdose and return to normal function at 15 minutes postdose. In addition, the hierarchical ranking order for the secondary endpoints was different between study 201 and 301. There were also some differences in the exclusion and inclusion criteria.

Trial Design

Basic Study Design
Study 301 was a Phase 3, double-blind, randomized, placebo controlled, multicenter, outpatient trial to evaluate the safety and efficacy of IN zavegepant versus placebo in the treatment of moderate or severe migraine attacks. Patients were randomized 1:1 to receive one Aptar UDS liquid spray device containing a single dose of 10 mg zavegepant or placebo. The total duration of the study was approximately 11 weeks. The study included a screening phase (lasting 3 to 28 days) and a treatment phase (of up to 45 days or until a subject experienced a migraine attack of moderate or severe intensity), followed by an EOT visit that occurred within 7 days of treatment (Figure 2). There was no option for a second dose. If a patient did not experience a migraine headache of moderate or severe intensity within 45 days after randomization, they were still required to complete all EOT visit procedures.

Figure 2 Study 301 Design Schematic



Source: Study 301 CSR, Figure 9-1

Diagnostic Criteria

The applicant used the diagnosis of migraine consistent with a diagnosis according to the ICHD-3.

Key Inclusion Criteria

1. Male or female patients age ≥18 years and older
2. At least one-year history of migraine with or without aura
3. No more than 8 migraine attacks of moderate or severe intensity per month within last 3 months prior to the screening visit
4. Migraine onset prior to age 50
5. Less than 15 days with headaches per month in each of the 3 months prior to screening
6. Subjects who were screen failures from this study (301) previously, could be considered for re-screening

Key Exclusion Criteria

1. Hemiplegic or basilar migraine
2. History of HIV, hepatitis B or C
3. History of uncontrolled, unstable, or recently diagnosed cardiovascular disease including

ischemic heart disease, coronary artery vasospasm, cerebral ischemia. Patients with a history of myocardial infarction, acute coronary syndrome, percutaneous coronary intervention, cardiac surgery, stroke, or transient ischemic attack during the 6 months prior to screening.

4. Uncontrolled hypertension or diabetes.
5. Diagnosis of major depression, pain syndromes, psychiatric conditions, dementia, or significant neurological disorders.
6. History of alcohol or drug abuse.
7. Acute or chronic treatment with over-the-counter or prescription nasal sprays.
8. History of nasal surgery in prior 6 months.
9. Evidence at screening of significant nasal conditions that may affect the administration or absorption.
10. Body mass index ≥40 kg/m^2
11. History of Gilbert's Syndrome or any other active hepatic or biliary disorder.
12. Female patients who are pregnant, lactating, breastfeeding, or unwilling or unable to use acceptable contraceptive method
13. Estimated glomerular filtration rate of ≤ 40 ml/min/1.73m2.
14. ECG findings including left or right bundle branch block, intraventricular conduction defect; QT interval > 470 msec; QRS≥150 msec.
15. Serum bilirubin >1.5 x ULN; neutrophil count ≤1000/uL; AST or ALT > 1.5xULN,

Dose Selection

Based on data from study 201, the 10 mg dose was selected. The applicant felt that based on study 201, a durable efficacy and favorable safety profile for zavegepant was established, with the 10 mg dose as the lowest fully efficacious dose to support Phase 3 clinical studies.

Study Treatments/Blinding

This was a double-blind placebo-controlled trial with 10 mg IN zavegepant, or matching placebo.

Assignment to Treatment

Randomization and treatment assignment occurred through the IWRS. All eligible patients who met study entry criteria were randomized across four treatment groups, in a 1:1 ratio to either zavegepant 10 mg IN, or matching placebo. The randomization was stratified by current use of preventive medications (yes/no).

Dose Modification/Dose Discontinuation

The dose of the IP was fixed and could not be adjusted.

Procedures and Schedule

The schedule of study procedures and assessments is summarized in Table 11. I have modified the table from the applicant's materials to only include key assessments.

Table 11 Schedule of Procedures and Assessments for Study 301

Procedure	Screening	Baseline/ Randomization Visit (Day 1)	Onset of moderate or severe migraine	Post Study Medication Administration: 15, 30, 45, 60 and 90 minutes 2, 3, 4, 6, 8, 24 and 48 hours	End of Treatment Visit
Physical Examination, ECG, Laboratory Testing, Urinalysis	X				X
Nasal Inspection	X	X			X
Vital Signs, Physical Measurements, Sheehan Suicidality Tracking Scale (S-STS)	X	X			X
Adverse Event and Serious Adverse Event Assessment	X	X	X	X	X
Pregnancy Test	X (Serum)	X (Urine)	X (Urine)		X (Serum)
Urine drug screen for drugs of abuse	X				X

Source: Study 301 Protocol version 4.0, Table 1

Dietary Restrictions/Instructions

N/A

Concurrent medications

The below medications are prohibited prior to randomization and during the course of this study or as specified.

1. St. John's Wort, butterbur root or extracts, modafinil (PROVIGIL®), barbiturate-containing products and marijuana.
2. Barbiturate-containing products (e.g., Fiercest, Fiorinal, butalbital, phenobarbital) should not be taken 14 days prior to randomization and throughout the study.
3. History of use of ergotamine medications on ≥10 days/month for ≥3 month
4. History of non-narcotic analgesic intake on ≥15 days per month for ≥3 month (e.g., acetaminophen, NSAIDs, gabapentin etc.) for other pain indications
5. Use of narcotic medication, such as morphine, codeine, oxycodone and hydrocodone.
6. Use of all acetaminophen or acetaminophen containing products at daily dosing levels
7. Muscle relaxants (baclofen is allowed as rescue medication).
8. Use of strong CYP3A4 inhibitors and inducers with BHV-3500 is prohibited during the study.
9. OTC or prescription topical nasal steroids, oxymetazoline, topical nasal antihistamines, topical nasal anticholinergics, and topical nasal mast cell stabilizers should not be taken within 14 days prior to the screening visit and throughout the study.
10. Prophylactic migraine medications are permitted to remain on therapy provided they have been on a stable dose for at least 3 months prior to study entry.
11. Use of CGRP antagonists.

Treatment Compliance

Accountability and compliance verification was documented. Subjects were counseled on the importance of taking the study drug as directed. Patients were to return for their end-of-treatment visit within 45 days of baseline visit if they did not have a qualifying migraine attack or take their study medication and return their study medication.

Rescue Medication

Other headache medications were prohibited during the first 2 hours postdose of study drug administration. If a patient did not experience migraine relief at 2 hours postdose, the patient was permitted to use only the following rescue medications: aspirin; ibuprofen; acetaminophen, up to 1,000 mg/day (this includes Excedrin® Migraine); Naprosyn (or any other type of NSAID); antiemetics (e.g., metoclopramide or promethazine); or baclofen.

If the migraine was relieved by study drug at 2 hours postdose but returned to a moderate or severe intensity level between 2 and 48 hours later, subjects were permitted to take the same rescue therapy as outlined above.

If after 48 hours postdose of study drug (and before returning to the clinical site for the EOT visit), patients were allowed to take their prescribed standard of care medications for treatment of migraine (including triptans if not contraindicated).

Subject Completion/Discontinuation/Withdrawal

Patients could withdrawal for any reason. All patients who discontinued were to comply with protocol specified end of treatment procedures.

Study Endpoints

Co-Primary Endpoints

1. Pain freedom at 2 hours postdose.
2. Freedom from the most bothersome symptom (MBS), associated with migraine, at 2 hours postdose.

Secondary Endpoints

1. Pain relief at 2 hours postdose.
2. Return to normal function at 2 hours postdose according to the FDS.
3. Sustained pain relief from 2 to 24 hours postdose.
4. Sustained pain relief from 2 to 48 hours postdose.
5. Sustained pain freedom from 2 to 24 hours postdose.
6. Sustained pain freedom from 2 to 48 hours postdose.
7. Phonophobia freedom at 2 hours postdose.
8. Photophobia freedom at 2 hours postdose.
9. Pain relief at 60 minutes postdose.
10. Return to normal function at 60 minutes postdose according to the FDS.
11. Pain relief at 30 minutes postdose.
12. Return to normal function at 30 minutes postdose according to the FDS.
13. Pain relief at 15 minutes postdose.
14. Return to normal function at 15 minutes postdose according to the FDS.
15. Rescue medication use within 24 hours postdose.
16. Nausea freedom at 2 hours postdose.
17. Pain relapse from 2 to 48 hours postdose.

Statistical Analysis Plan

Analysis populations

1. Enrolled analysis set: Patients who signed an ICF and were assigned a subject identification number.
2. Randomized analysis set: Patients in the enrolled analysis set who received a randomized treatment assignment from the IWRS.
3. Efficacy analysis set: Patients in the randomized analysis set who 1) were randomized only once, 2) had a migraine of moderate or severe pain intensity at the time of dosing, 3) took study drug, and 4) had postdose efficacy data.
4. Safety analysis set: Patients in the enrolled analysis set who took study drug.
5. Full analysis set: Patients in the randomized or safety analysis set. If there were nonrandomized patients who received study drug, then the as-randomized treatment group of “not randomized” was included for the full analysis set.

Sample Size Estimation

The applicant anticipated that if 90% of the 700 subjects randomized to each treatment group would have a qualifying migraine in the allotted time period, resulting in approximately 630 subjects evaluable for efficacy in each treatment group. The sample size calculation was based on results from the Phase 2/3 dose-ranging study 201. The response rates for the pooled zavegepant 10 mg and 20 mg groups, and for the placebo group, in study 201 were 22.8% and 15.5%, respectively, for pain freedom at 2 hours postdose, and 42.2% and 33.7%, respectively, for MBS freedom at 2 hours postdose.

A total sample size of 1,260 evaluable subjects (630 per group) would provide approximately 91% power for the co-primary endpoint of pain freedom at 2 hours postdose, approximately 88% power for the co-primary endpoint of MBS freedom at 2 hours postdose, and approximately 80% power to detect a difference between treatment groups for both endpoints jointly.

Hypothesis Testing

Type I error was controlled in this study by using a hierarchical gate-keeping procedure. First, the two co-primary endpoints were tested. If both co-primary endpoints were found to be significant, then secondary endpoints were tested in a fixed sequence. Each co-primary endpoint was tested for superiority to placebo at a 2-sided alpha level of 0.05 without further adjustment for multiplicity.

If a test in the hierarchy was not significant, then it, and any further tests on endpoints in the sequence, would have p-values presented only for descriptive purposes, and no conclusions would be drawn from those results.

Pre-Specified Methods for Handling Missing Data

Subjects with missing data at a single time point were classified as failures. This missing data imputation method was applied to endpoints based on data from a single time point. For the coprimary endpoints, a patient with missing data was considered a treatment failure.

Patients taking rescue medication at or before the 2-hour postdose time point are imputed as failures.

Protocol Amendments

There were four versions of the protocol, with the original protocol was issued on February 3, 2020, per the applicant. The second version of the protocol was created on September 22, 2020. This version updated the name from vazegepant to zavegepant. The version also clarified contraception guidance and provided COVID-19 study visit requirements. Changes in the third version, which were made on April 26, 2021, included updating the exclusion criteria related to chronic pain syndromes and related to patients who previously participated in BHV-3500 study.

Protocol version 4 was submitted on September 12, 2019 and added the inclusion criterion that subjects can be rescreened if the ineligibility was due to one of the eligibility items adjusted in protocol version 4 or who are reasonably expected to be eligible. It also removed the exclusion criterion of history of gastric, or small intestinal surgery, or other disease or condition that causes malabsorption, removed HbA1c exclusion criterion, updated BMI exclusion to > 40kg/m^2, and updated the exclusion criteria for serum bilirubin, AST and ALT to >1.5xULN.

6.2.2. Study Results

Compliance with Good Clinical Practices

The applicant states that the study was conducted in compliance with the protocol, GCP guidelines, and all applicable regulations, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations (title 21), any IRB/IEC requirements relative to clinical studies.

Financial Disclosure

Please see Appendix 13.2.

Patient Disposition

Enrolled: 1978
Randomized: 1405 (placebo: 702, zavegepant 10 mg: 703)
Safety (Patients in the enrolled analysis set who took study drug): Received at least 1 dose of double-blind study drug: 1282 (placebo: 653, zavegepant 10 mg: 629)
Efficacy (Patients in the randomized analysis set who (1) are randomized only once, (2) have a migraine of moderate or severe pain intensity at the time of dosing, (3) take study drug, and (4) have postdose efficacy data): 1269 (placebo: 646, zavegepant 10 mg: 623)
Full (Patients in the randomized or safety analysis set): 1405 (placebo: 702, zavegepant 10 mg: 703)

Of the randomized patients, 1269 patients (91.2%) were included in the efficacy analysis set. One hundred twenty-three patients were randomized but not treated, and thirteen patients were treated but were not in the efficacy analysis set. Of those seven patients, all were excluded from the efficacy analysis set because they did not have post-baseline efficacy data.

Protocol Violations/Deviations

Significant protocol deviations are defined as study conduct that differs significantly from the current protocol, including GCP non-compliance. A relevant protocol deviation was defined as a deviation from the protocol which is programmed from the database, and which could potentially affect the interpretability of the study results. The relevant protocol deviations appear to be well balanced and low, and therefore are not expected to affect the primary

Table 12 Relevant Protocol Deviations in Randomized Patients for Study 301

Protocol Deviation	Placebo N=702 n(%)	10 mg N=703 n(%)
Rescue medication usage error	47 (6.7)	48 (6.8)
Prohibited non-study medication usage	25 (3.6)	25 (3.6)
Study drug dosing error	12 (1.7)	9 (1.3)
Prophylactic migraine medication started or stopped from 3 months before informed consent to randomization	6 (0.9)	5 (0.7)

Source: Study 301 CSR, Table 14.1.4

Table of Demographic Characteristics

No significant baseline imbalances in the demographic characteristics were noted between placebo and treatment groups in the mITT population (Table 13).

Table 13 Study 301: Study 301: Demographic Characteristics of the Efficacy Analysis Set

Demographic Parameters	Placebo (N=646) n(%)	10 mg (N=623) n(%)
Sex		
Male	100 (15.5)	117 (18.8)
Female	546 (84.5)	506 (81.2)
Age		
Mean years (SD)	40.9 (13.22)	40.8 (13.46)
Median (years)	40.0	40.0
Min, max (years)	18, 73	18, 76
Age Group*		
18 to 40	319 (49.4)	299 (48.0)
41 to 64	294 (45.5)	299 (48.0)
65+	33 (5.1)	25 (4.0)
Race		
White	540 (83.6)	511 (82.0)
Black or African American	83 (12.8)	85 (13.6)
Asian	15 (2.3)	20 (3.2)
American Indian or Alaska Native	2 (0.3)	0
Native Hawaiian/ Pacific Islander	1 (0.2)	2 (0.3)

Other/Multiple	5 (0.8)	5 (0.8)
Ethnicity		
Hispanic or Latino	145 (22.4)	112 (18.0)
Not Hispanic or Latino	501 (77.6)	511 (82.0)
Concomitant preventive medication		
Yes	82 (12.7)	88 (14.1)
Body Mass Index (BMI) kg/m²		
Mean (SD)	27.46 (5.040)	27.43 (5.012)
Median	27.10	27.10
Min, Max	15.9, 40.1	15.2, 39.9

Source: Study 301 CSR, Table 10-2

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

No significant imbalances in the migraine history characteristics for the efficacy analysis set were noted between placebo and treatment groups (Table 14).

Table 14 Study 301: Migraine History for the Efficacy Analysis Set

	Placebo (N=646)	10 mg (N=623)
Number of moderate to severe migraines per month by history		
Mean (SD)	4.7 (1.81)	4.6 (1.81)
Median	4.0	4.0
Min, Max	2, 8	2, 8
Most bothersome symptom (MBS)		
Nausea n(%)	148 (22.9)	165 (26.5)
Phonophobia n(%)	92 (14.2)	98 (15.7)
Photophobia n(%)	406 (62.8)	360 (57.8)
Primary migraine type		
Without aura n(%)	418 (64.7)	417 (66.9)
With aura n(%)	228 (35.3)	206 (33.1)

Source: Study 301 CSR, Table 14.1.5.2A

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Patients were instructed to return the study medication if they did not experience a moderate to severe migraine or did not take the study drug within 45 days of baseline visit

Overall, 12.1% (155 patients) of the safety analysis set used concomitant preventive medications for migraine, with 13.2% (83 patients) of the 10 mg zavegepant group and 11.0%

(72 patients) of the placebo group took concomitant preventive medications for migraine. The most common were topiramate (82 patients [6.4%]) and non-selective monoamine reuptake inhibitors (20 patients [1.6%]).

Rescue medication in the efficacy analysis set was taken more in the placebo group (38.2%) than the 10 mg zavegepant group (31.8%).

Reviewer comment: The groups for concomitant prophylactic medications do not appear to have a significant imbalance.

Efficacy Results – Primary Endpoint

The co-primary endpoints for study 301 were:

1. Pain freedom at 2 hours postdose.
2. Freedom from the MBS associated with migraine at 2 hours postdose

The co-primary endpoints were evaluated for efficacy by comparing zavegepant-treated patients versus placebo-treated patients. The efficacy analysis set was used for the efficacy analyses. The 10 mg dose of zavegepant demonstrated statistically significant results for both co-primary efficacy endpoints compared to placebo (Table 15). Statistical reviewer, Dr. Yi Le, has verified these results and has confirmed the applicant's analysis and calculation of the co-primary efficacy endpoints.

Table 15 Study 301: Results of Co-Primary Efficacy Endpoints – Efficacy Analysis Set

	Placebo (N = 646)	10 mg (N = 623)
Pain Freedom at 2 hours postdose		
n (%)	96 (14.9)	147 (23.6)
Percentage difference (Zavegepant – Placebo)[a]	N/A	8.8
(95% CI)	N/A	(4.5, 13.1)
p-value	N/A	<0.001 *
MBS freedom at 2 hours postdose		
n (%)	201 (31.1)	247 (39.6)
Percentage difference (Zavegepant – Placebo)[a]	N/A	8.7
(95% CI)	N/A	(3.4, 13.9)
p-value	N/A	0.0012*

Source: Study 301 CSR, Table 11-1
[a]Stratified by prophylactic migraine medication use at randomization with CMH weighting
*Statistically significant

Data Quality and Integrity

No quality data issues were identified during the review of study 301. The data and analysis quality were adequate, and the statistical reviewer performed an independent review using the applicant's datasets. Please see Dr. Yi Le's statistical review.

Efficacy Results – Secondary and other relevant endpoints

The secondary efficacy endpoints were tested hierarchically in the following order:

1. Pain relief at 2 hours postdose.
2. Return to normal function at 2 hours postdose according to the FDS.
3. Sustained pain relief from 2 to 24 hours postdose.
4. Sustained pain relief from 2 to 48 hours postdose.
5. Sustained pain freedom from 2 to 24 hours postdose.
6. Sustained pain freedom from 2 to 48 hours postdose.
7. Phonophobia freedom at 2 hours postdose.
8. Photophobia freedom at 2 hours postdose.
9. Pain relief at 60 minutes postdose.
10. Return to normal function at 60 minutes postdose according to the FDS.
11. Pain relief at 30 minutes postdose.
12. Return to normal function at 30 minutes postdose according to the FDS.
13. Pain relief at 15 minutes postdose.
14. Return to normal function at 15 minutes postdose according to the FDS.
15. Rescue medication use within 24 hours postdose.
16. Nausea freedom at 2 hours postdose.
17. Pain relapse from 2 to 48 hours postdose.

In study 301, 10 mg of zavegepant demonstrated statistically significant findings for the first 13 secondary endpoints in the hierarchy (Table 16 and 17). The secondary endpoint of return to normal function at 15 minutes postdose according to the FDS was not statistically significant, and therefore due to hierarchical testing procedure all of the following secondary endpoints were not statistically significant. The secondary endpoint of rescue medication use within 24 hours postdose was nominally significant.

Table 16 Study 301 Results of Secondary Efficacy Endpoints

	Placebo (N = 646)	10 mg (N = 623)
(1) Pain relief at 2 hours postdose		
n (%)	321 (49.7)	366 (58.7)
Percentage difference (Zavegepant – Placebo) [a]	N/A	9.0
(95% CI)	N/A	(3 6, 14.5)
p-value	N/A	0.0012*
(2) Return to normal function at 2 hours postdose		

n (%)	152 (25.6)	204 (35.8)
Percentage difference (Zavegepant – Placebo) [a]	N/A	10.2
(95% CI)	N/A	(5 0, 15.5)
p-value	N/A	0.0001*
(3) Sustained pain relief from 2 to 24 hours postdose		
n (%)	213 (33.0)	253 (40.6)
Percentage difference (Zavegepant – Placebo) [a]	N/A	7.6
(95% CI)	N/A	(2 3, 12.9)
p-value	N/A	0.0048*
(4) Sustained pain relief from 2 to 48 hours postdose		
n (%)	191 (29.6)	225 (36.1)
Percentage difference (Zavegepant – Placebo) [a]	N/A	6.5
(95% CI)	N/A	(1 4, 11.7)
p-value	N/A	0.0130*
(5) Sustained pain freedom from 2 to 24 hours postdose		
n (%)	63 (9.8)	91 (14.6)
Percentage difference (Zavegepant – Placebo) [a]	N/A	4.9
(95% CI)	N/A	(1.3, 8.5)
p-value	N/A	0.0076*
(6) Sustained pain freedom from 2 to 48 hours postdose		
n (%)	56 (8.7)	77 (12.4)
Percentage difference (Zavegepant – Placebo) [a]	N/A	3.7
(95% CI)	N/A	(0.3, 7.1)
p-value	N/A	0.0308*
(7) Phonophobia freedom at 2 hours postdose		
n (%)	139 (32.7)	167 (41.0)
Percentage difference (Zavegepant – Placebo) [a]	N/A	8.3
(95% CI)	N/A	(1 8, 14.9)
p-value	N/A	0.0123*
(8) Photophobia freedom at 2 hours postdose		
n (%)	167 (28.5)	207 (37.1)
Percentage difference (Zavegepant – Placebo) [a]	N/A	8.6
(95% CI)	N/A	(3 2, 14.1)
p-value	N/A	0.0018*
(9) Pain relief at 60 minutes postdose		
n (%)	241 (37.3)	270 (43.3)
Percentage difference (Zavegepant – Placebo) [a]	N/A	6.0
(95% CI)	N/A	(0 6, 11.4)
p-value	N/A	0.0293*

(10) Return to normal function at 60 minutes postdose		
n (%)	92 (15.5)	115 (20.2)
Percentage difference (Zavegepant – Placebo) [a]	N/A	4.7
(95% CI)	N/A	(0.3, 9.1)
p-value	N/A	0.0362*
(11) Pain relief at 30 minutes postdose		
n (%)	131 (20.3)	190 (30.5)
Percentage difference (Zavegepant – Placebo) [a]	N/A	10.2
(95% CI)	N/A	(5 5, 15.0)
p-value	N/A	<0.0001*
(12) Return to normal function at 30 minutes postdose		
n (%)	36 (6.1)	60 (10.5)
Percentage difference (Zavegepant – Placebo) [a]	N/A	4.4
(95% CI)	N/A	(1.3, 7.6)
p-value	N/A	0.0059*
(13) Pain relief at 15 minutes postdose		
n (%)	52 (8.0)	99 (15.9)
Percentage difference (Zavegepant – Placebo) [a]	N/A	7.8
(95% CI)	N/A	(4 2, 11.3)
p-value	N/A	0.0001*
(14) Return to normal function at 15 minutes postdose		
n (%)	12 (2.0)	19 (3.3)
Percentage difference (Zavegepant – Placebo) [a]	N/A	1.3
(95% CI)	N/A	(- .6, 3.1)
p-value	N/A	0.1826
(15) Rescue medication use within 24 hours postdose		
n (%)	230 (35.8)	184 (29.7)
Percentage difference (Zavegepant – Placebo)[a]	N/A	-6.1
(95% CI)	N/A	(-1 .3, -1.0)
p-value	N/A	0.0194**
(16) Nausea freedom at 2 hours postdose		
n (%)	206 (50.9)	199 (52.4)
Percentage difference (Zavegepant – Placebo) [a]	N/A	1.5
(95% CI)	N/A	(- .5, 8.5)
p-value	N/A	0.6753
(17) Pain relapse from 2 to 48 hours postdose		
n (%)	34 (35.4)	61 (40.8)
Percentage difference (Zavegepant – Placebo)[a]	N/A	5.4
(95% CI)	N/A	(-7.0, 17.8)

p-value	N/A	0.3944

Source: Study 301 CSR, Table 11-2
*Statistically significant base on testing hierarchy
**Nominal p-value

Table 17 Study 301: Secondary Endpoints Reaching Statistical and Nominal Significance

	10 mg
Pain relief at 2 hours postdose.	x
Return to normal function at 2 hours postdose according to the FDS.	x
Pain relief from 2 to 24 hours postdose.	x
Sustained pain relief from 2 to 48 hours postdose.	x
Sustained pain freedom from 2 to 24 hours postdose.	x
Sustained pain freedom from 2 to 48 hours postdose.	x
Phonophobia freedom at 2 hours postdose.	x
Photophobia freedom at 2 hours postdose.	x
Pain relief at 60 minutes postdose.	x
Return to normal function at 60 minutes postdose according to the FDS.	x
Pain relief at 30 minutes postdose.	x
Return to normal function at 30 minutes postdose according to the FDS.	x
Pain relief at 15 minutes postdose.	x
Return to normal function at 15 minutes postdose according to the FDS.	
Rescue medication use within 24 hours postdose.	y
Nausea freedom at 2 hours postdose.	
Pain relapse from 2 to 48 hours postdose	

x=statistically significant
y=nominally significant

Reviewer comments: Based on testing hierarchy there are 13 secondary endpoints that met statistical significance. Of those 13, the following 5 secondary endpoint would be clinically meaningful and therefore I recommend including in the PI:

1. *Pain relief at 2 hours*
2. *Return to normal function at 2 hours*
3. *Sustained pain freedom from 2 to 48 hours*
4. *Freedom from photophobia at 2 hours*
5. *Freedom from phonophobia at 2 hours*

Sustained pain freedom from 2 to 24 hours could also be considered given that it was also a statistically significant secondary endpoint, however if sustained pain freedom from 2 to 48 hours is included then the 2 to 24 hours interval would not be as informative.

Dose/Dose Response

Sensitivity Analyses

The applicant performed multiple sensitivity analyses of the co-primary endpoints. One of the analyses was a “complete cases” analysis in which patients who had missing data at the two-hour postdose time point were excluded (Table 18).

Table 18 Study 301: "Complete Cases" Sensitivity Analysis

	Placebo (N = 401)	10 mg (N = 391)
Pain freedom at 2 hours postdose		
n/N (%)	96/632 (15.2)	147/614 (23.9)
Percentage difference (BHV-3500 - Placebo)		8.8
(95% CI)		(4.4, 13.2)
P-value		<0.0001
MBS freedom at 2 hours postdose		
n/N (%)	201/632 (31.8)	247/615 (40.2)
Percentage difference (BHV-3500 - Placebo)		8.5
(95% CI)		(3.2, 13.8)
P-value		0.0017

Source: Study 301 CSR, Tables 14.2.1.1E and 14.2.1.2E

Reviewer comment: The complete cases sensitivity analysis performed by the applicant support the results of the primary endpoint analysis for both co-primary endpoints.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The integrated review of effectiveness will examine study 201 and 301. The 10 mg dose will be the focus of the review as it is the proposed marketed dose.

7.1.1. Primary Endpoints

The same co-primary endpoints of pain freedom at 2 hours postdose and MBS freedom at 2 hours postdose were used in both study 201 and 301. These co-primary endpoints are consistent with the Guidance for Industry *Migraine: Developing Drugs for Acute Treatment.* Study 201 evaluated three doses of zavegepant compared to placebo, while study 301 included

only the 10 mg dose. Both studies demonstrated statistical significance of 10 mg zavegepant over placebo for the co-primary endpoints. In addition, study 201 demonstrated statistical significance for the co-primary endpoints at the 20 mg dose, but not at the 5 mg dose.

Table 19 Summary Findings for the Co-Primary Endpoints for Studies 201 and 301

	Study 201				Study 301	
	PBO	5 mg	10 mg	20 mg	PBO	10 mg
Pain freedom at 2 hours postdose (%)	15.5	19.6	22.5	23.1	14.9	23.6
Percentage difference		4.2	7.0	7.7		8.8
p-value		0.1214	0.0113*	0.0055*		<0.001*
MBS freedom at 2 hours postdose (%)	33.7	39.0	41.9	42.5	31.1	39.6
Percentage difference		5.4	8.3	8.9		8.7
p-value		0.1162	0.0155*	0.0094*		0.0012*

Source: Study 201 CSR, Table 10-1 and Study 301 CSR, Table 11-1
PBO=placebo
*Statistical significance

7.1.2. Secondary and Other Endpoints

Study 301 had the same 15 secondary endpoints of study 201. In addition, study 301 had two additional secondary endpoints of pain relief at 15 minutes postdose and return to normal function at 15 minutes postdose. The hierarchy of secondary endpoints in study 201 and study 301 were different.

The first, secondary endpoint in study 201 was not statistically significant for the 10 mg and 20 mg groups and therefore based on testing hierarchy the rest of the following secondary endpoints were not statistically significant. Therefore, I recommend that none of the secondary endpoints from study 201 should be described in the PI.

The first 13 secondary endpoints in study 301 were statistically significant, which were as follows:

1. Pain relief at 2 hours postdose.
2. Return to normal function at 2 hours postdose according to the FDS.
3. Sustained pain relief from 2 to 24 hours postdose.
4. Sustained pain relief from 2 to 48 hours postdose.
5. Sustained pain freedom from 2 to 24 hours postdose.
6. Sustained pain freedom from 2 to 48 hours postdose.
7. Phonophobia freedom at 2 hours postdose.
8. Photophobia freedom at 2 hours postdose.

9. Pain relief at 60 minutes postdose.
10. Return to normal function at 60 minutes postdose according to the FDS.
11. Pain relief at 30 minutes postdose.
12. Return to normal function at 30 minutes postdose according to the FDS.
13. Pain relief at 15 minutes postdose.

Of these, I would recommend five key secondary endpoints to be included in the PI for study 301 (Table 20).

Table 20 Study 301: Summary of the Treatment Effect for Key Secondary Endpoints

	Placebo (N = 646)	10 mg (N = 623)
Pain relief at 2 hours postdose		
n (%)	321 (49.7)	366 (58.7)
Percentage difference (Zavegepant – Placebo) [a]	N/A	9.0
Return to normal function at 2 hours postdose		
n (%)	152 (25.6)	204 (35.8)
Percentage difference (Zavegepant – Placebo) [a]	N/A	10.2
Sustained pain freedom from 2 to 48 hours postdose		
n (%)	56 (8.7)	77 (12.4)
Percentage difference (Zavegepant – Placebo) [a]	N/A	3.7
Phonophobia freedom at 2 hours postdose		
n (%)	139 (32.7)	167 (41.0)
Percentage difference (Zavegepant – Placebo) [a]	N/A	8.3
Photophobia freedom at 2 hours postdose		
n (%)	167 (28.5)	207 (37.1)
Percentage difference (Zavegepant – Placebo) [a]	N/A	8.6

Source: Reviewer created table

7.1.3. Subpopulations

The applicant performed subpopulation analyses on pooled data of studies 201 and 301 for the 10 mg dose. These analyses included subpopulation analyses based on age, sex, BMI, and prophylactic migraine medication usage. Below the applicant's results of the pooled subpopulation analyses (Tables 21-24).

Age

The applicant performed a subgroup analysis by age of pooled data for the co-primary endpoints of pain freedom at 2 hours postdose and MBS freedom at 2 hours (Table 21).

Table 21 Study 201 and 301: Pooled Subgroup Efficacy Analyses for Co-Primary Endpoints by Age

		Pain Freedom at 2 hours Postdose		MBS Freedom at 2 hours Postdose	
		10 mg N=1,014	Placebo N=1,047	10 mg N=1,014	Placebo N=1,047
Age (years)					
< 40	N	485	522	485	522
	Responders, n(%)	129 (26.6)	81 (15.5)	201 (41.4)	163 (31.2)
	Treatment effect (%)	11.1		10.2	
≥ 40	N	529	525	529	525
	Responders, n(%)	106 (20)	77 (14.7)	210 (39.7)	173 (33)
	Treatment effect (%)	5.4		6.7	

Source: Summary of Clinical Efficacy (SCE), Table 10

Reviewer comment: Both groups (<40 and ≥40 years) had a similar sample size. There does appear to be a lesser treatment effect in the ≥40-year-old population. Although no conclusion can be drawn, it is interesting given the context that in some other reviews of CGRP receptor antagonists there was no treatment effect seen in older populations.

Sex

The applicant performed a subgroup analysis by sex of pooled data for the co-primary endpoints of pain freedom at 2 hours postdose and MBS freedom at 2 hours (Table 22).

Table 22 Study 201 and 301: Pooled Subgroup Efficacy Analyses for Co-Primary Endpoints by Sex

		Pain Freedom at 2 hours Postdose		MBS Freedom at 2 hours Postdose	
		10 mg N=1,014	Placebo N=1,047	10 mg N=1,014	Placebo N=1,047
Sex					
Female	N	839	884	839	884

	Responders, n(%)	195 (23.2)	129 (14.6)	350 (41.7)	286 (32.4)
	Treatment effect (%)	8.6		9.3	
Male	N	175	163	175	163
	Responders, n(%)	40 (22.9)	29 (17.8)	61 (34.9)	50 (30.7)
	Treatment effect (%)	4.6		4.2	

Source: SCE, Table 10

Reviewer comment: There does appear to be a lesser treatment effect in male patients versus female patients for the co-primary endpoints. However, the treatment effect appears to be present.

Prophylactic Migraine Medication Use

The applicant performed a subgroup analysis by use of prophylactic migraine medications use of pooled data for the co-primary endpoints of pain freedom at 2 hours postdose and MBS freedom at 2 hours postdose (Table 23).

Table 23 Study 201 and 301: Pooled Subgroup Efficacy Analyses for Co-Primary Endpoints by Prophylactic Migraine Medication Use

		Pain Freedom at 2 hours Postdose		MBS Freedom at 2 hours Postdose	
		10 mg N=1,014	Placebo N=1,047	10 mg N=1,014	Placebo N=1,047
Prophylactic Migraine Medication Use					
Yes	N	138	136	138	136
	Responders, n(%)	30 (21.7)	17 (12.5)	57 (41.3)	33 (24.3)
	Treatment effect (%)	9.3		17.5	
No	N	876	911	876	911
	Responders, n(%)	205 (23.4)	141 (15.5)	354 (40.4)	303 (33.3)
	Treatment effect (%)	7.9		7.1	

Source: SCE, table 10

Reviewer comment: In patients using migraine prophylaxis there was a greater treatment effect especially in the co-primary endpoint of MBS freedom at 2 hours postdose. The group of patients who used prophylactic migraine medications was significantly smaller and therefore it is difficult to draw conclusions. Overall, the treatment effect is present whether patients were on migraine prophylaxis or not.

BMI
The applicant performed a subgroup analysis by BMI of pooled data for the co-primary endpoints of pain freedom at 2 hours postdose and MBS freedom at 2 hours (Table 24).

Table 24 Study 201 and 301: Pooled Subgroup Efficacy Analyses for Co-Primary Endpoints by BMI

		Pain Freedom at 2 hours Postdose		MBS Freedom at 2 hours Postdose	
		10 mg N=1,014	Placebo N=1,047	10 mg N=1,014	Placebo N=1,047
BMI (kg/m2)					
< 25	N	344	343	344	343
	Responders, n(%)	78 (22.7)	53 (15.5)	139 (40.4)	109 (31.8)
	Treatment effect (%)	7.2		8.6	
≥ 25 to < 30	N	349	362	349	362
	Responders, n(%)	84 (24).1	48 (13.3)	143 (41)	115 (31.8)
	Treatment effect (%)	10.8		9.2	
≥30	N	321	342	321	342
	Responders, n(%)	73 (22.7)	57 (16.7)	129 (40.2)	112 (32.7)
	Treatment effect (%)	6.2		7.4	

Source: SCE, table 10

Reviewer comment: The sample size for each BMI category (<25, ≥25 to <30, and ≥30) appear to be similar. The ≥25 to <30 subgroup appears to have the highest treatment effect, while the lower and higher BMI subgroups had a slightly smaller treatment effect. Overall, there appears to be a treatment effect is present across different BMIs.

7.1.4. Dose and Dose-Response

In study 201 there were three doses evaluated. This dose finding study demonstrated that the 10 mg and 20 mg dose was effective while the 5 mg dose was not. However, the dose response was flat between the 10 mg and 20 mg doses, with response rates of 23.2% and 24% for pain freedom at 2 hours postdose, respectively, and 43.3% and 44.2% for MBS freedom at 2 hours postdose, respectively. The 10 mg dose was selected by the applicant as the optimal therapeutic dose since it minimizes systemic exposure of zavegepant while providing efficacy. It

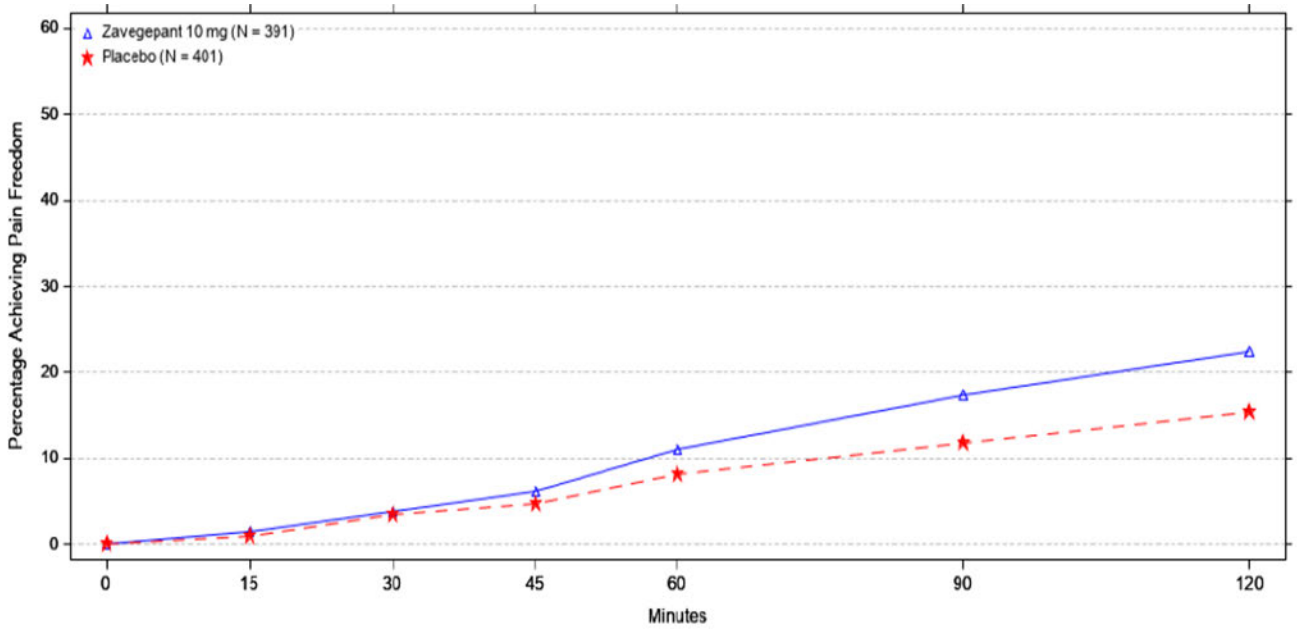
appears appropriate from an efficacy standpoint to utilize the 10 mg dose as the marketed dose.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Onset of Efficacy Effects

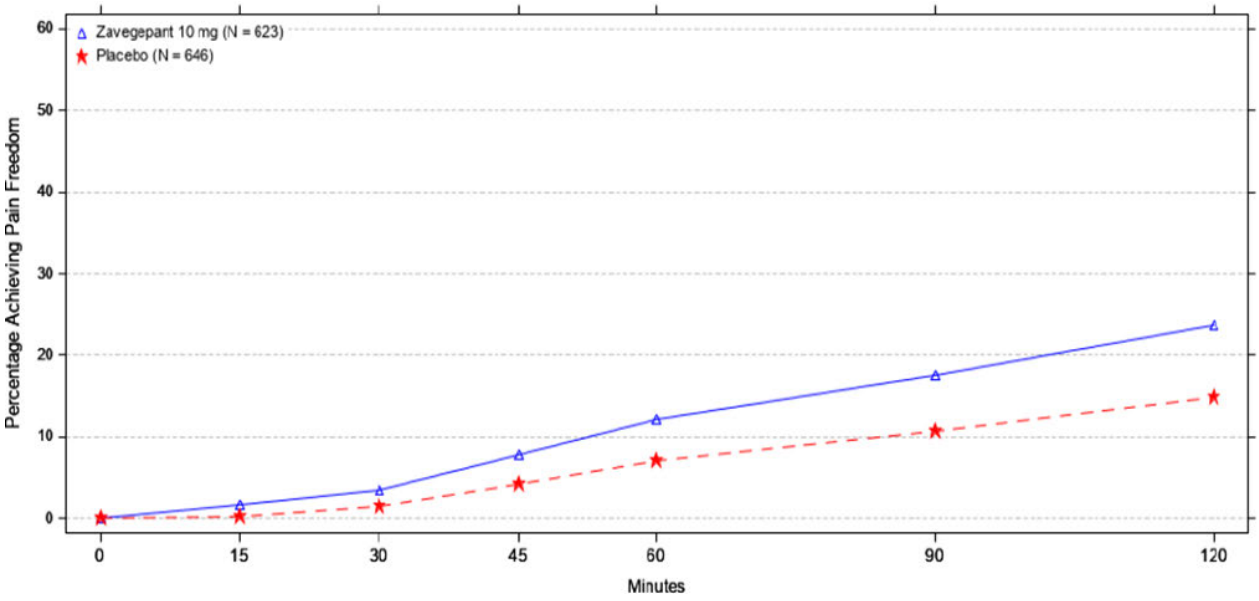
Below are the longitudinal plots of pain freedom through 2 hours postdose for study 201, study 301, and pooled data (Figure 3, 4, 5). The median T_{max} of IN zavegepant was measured to be 0.54 hours. In both studies, the applicant conducted analyses of pain freedom at multiple timepoints (15, 30, 45, 60, and 90 minutes postdose) through 2 hours postdose. No formal assessment of onset of efficacy can be made. In study 301, pain freedom at 15 minutes for zavegepant versus placebo (p=0.0058) was statistically significant and continued to be statistically significant through 2 hours. In study 201, there was not a statistically significant difference till the 2 hours postdose.

Figure 3 Study 201: Longitudinal Plot of Pain Freedom through 2 Hours Postdose



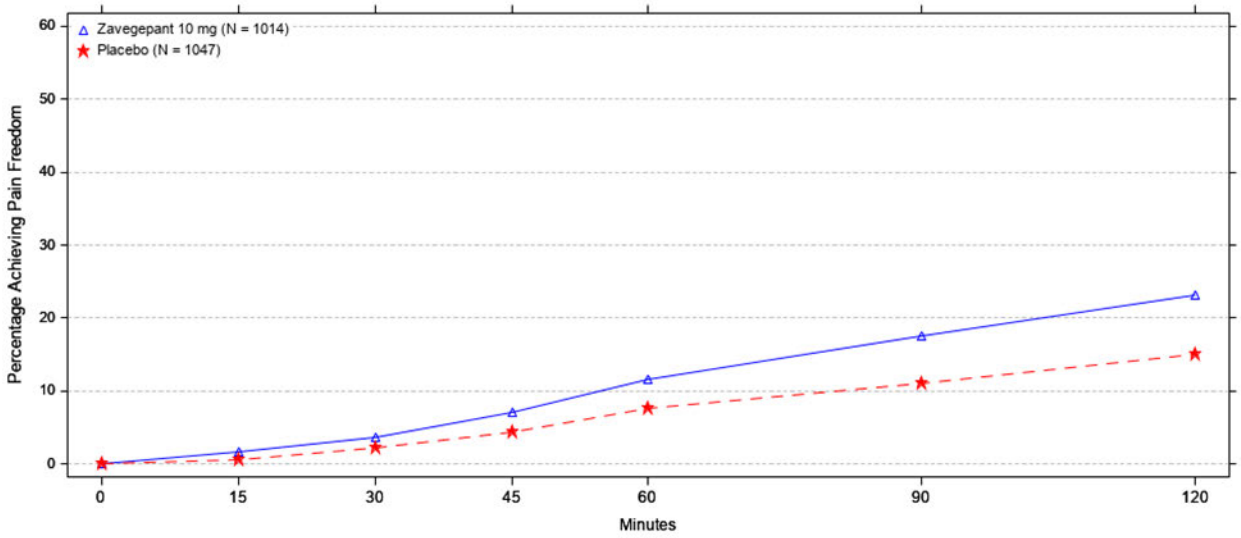
Source: SCE, Appendix 2.12I

Figure 4 Study 301: Longitudinal Plot of Pain Freedom through 2 Hours Postdose



Source: SCE, Appendix 2.12J

Figure 5 Pooled Data: Longitudinal Plot of Pain Freedom through 2 Hours Postdose



Source: SCE, Figure 4

Durability of Efficacy Effects

The secondary endpoint of sustained pain freedom from 2 to 48 hours was evaluated in study 201 and 301. Sustained pain freedom is defined as pain freedom with no intervening rescue medication, and pain level of none at all described time points. In study 201 and study 301,

sustained pain freedom from 2 to 48 hours was nominally significant and statistically significant, respectively. With 13.8% of patients who received 10 mg zavegepant in study 201 and 12.4% of patients who received 10 mg zavegepant in study 301 experiencing sustained pain freedom from 2 to 48 hours. This is in compared to 7.5% and 8.7% of placebo patients in study 201 and 301, respectively. With pooled data, 12.9% of patients receiving 10 mg zavegepant experienced sustained pain freedom from 2 to 48 hours compared to 8.2 % in the placebo arms.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Overall, the applicant attempted to include a population that would benefit from use of IN zavegepant. However, there are subpopulations that may not had a large enough sample size to reveal differences in terms of efficacy from the entire study population. There were 45 patients in the 10 mg zavegepant group that were 65 year and older. In addition, there was a decreased treatment effect in patients 40 year and older. There also appears to be a decrease in treatment effect in the male population versus the female population. This could be of concern given that around 10% of men in the general population experience migraines.

7.3. Integrated Assessment of Effectiveness

The applicant has submitted evidence to meet the statutory evidentiary standard. Both study 201 and study 301 provide evidence that 10 mg of IN zavegepant is an effective dose for the acute treatment of migraine. Study 201 also demonstrated that a 20 mg dose of IN zavegepant is effective for the acute treatment of migraine, however that 20 mg dose does not appear to offer a clinically meaningful greater effect than the 10 mg dose. Both study 201 and 301 demonstrated statistical significance for the co-primary endpoints of pain freedom at 2 hours postdose and MBS freedom at 2 hours postdose. In further support of the efficacy of zavegepant, multiple key secondary endpoints for studies 201 and 301 were either statistically significant or nominally significant.

Study 301 found statistical significance for the following key secondary endpoints: Pain relief at 2 hours, return to normal function at 2 hours, sustained pain freedom from 2 to 48 hours, freedom from photophobia at 2 hours, and freedom from phonophobia at 2 hours.

Study 201 failed to demonstrate statistical significance for the first, secondary endpoint of pain relief at 2 hours postdose. Therefore, based on testing hierarchy all the rest of the 15 secondary endpoints were not statistically significant. There was nominal significance for the key secondary endpoints of pain relief at 2 hours postdose, return to normal function at 2 hours postdose, freedom from phonophobia at 2 hours postdose, and sustained pain freedom from 2 to 48 hours postdose.

In terms of product labeling, I recommend including the co-primary endpoints for both studies.

For study 201, I do not recommend including any secondary endpoints since none were statistically significant. For study 301, I recommend including the following secondary endpoints:

1. Pain relief at 2 hours
2. Return to normal function at 2 hours
3. Sustained pain freedom from 2 to 48 hours
4. Freedom from photophobia at 2 hours
5. Freedom from phonophobia at 2 hours

8. Review of Safety

8.1. Safety Review Approach

Studies 106, 201, 202, and 301 will be included in the safety review. The applicant defined the safety analysis set as enrolled patients who receive ≥ 1 dose of study drug (zavegepant or placebo), i.e., non-missing study drug start date. This analysis set is used to assess study population, exposure, and on-treatment safety.

The applicant grouped the safety data as the following (all studies will be referred to by the last three digits of the study name):

1. Single-dose studies in subjects with migraine (BHV3500-301 and BHV3500-201, zavegepant 10 mg IN)
2. Ongoing long-term safety study in subjects with migraine (BHV3500-202, zavegepant 10 mg IN), Completed with 120-day SUR. Throughout the review data from this study will include the 120-day SUR unless otherwise indicated.
3. Daily dosing safety study in healthy subjects (BHV3500-106, 100 mg oral formulation)
4. Phase 1 studies in healthy subjects with zavegepant 10 mg IN (BHV3500-101 single ascending dose [SAD] healthy subjects; BHV3500-102, multiple ascending dose [MAD] healthy subjects)
5. Safety of zavegepant in special populations (intrinsic factors [hepatic impairment: BHV3500-108]; extrinsic factors [DDI: oral contraceptive, BHV3500-109; sumatriptan, BHV3500-110; rifampin and itraconazole, BHV3500-111])
6. Safety of zavegepant with other formulations/doses/indications
    a. Safety in healthy subjects (zavegepant 50 mg ODT: BHV3500-103; intravenous [^{14}C]-zavegepant 5 mg: BHV3500-104; zavegepant 50, 100, or 200 mg soft gelatin capsule or 50, 100, or 200 mg ODT + DDM: BHV3500-107)
    b. Phase 1 studies in subjects with migraine (zavegepant 10 or 20 mg IN: BHV3500-105)

Table 25 Clinical Studies Contributing to the Integrated Review of Safety

Study BHV3500-	Dose(s)	Patients in double-blind safety set	Patients in open-label safety set
Group 1			
201	Placebo, zavegepant 5 mg, 10 mg, or 20 mg	Placebo (420) 5 mg (418) 10 mg (417) 20 mg (418)	N/A
301	Placebo or zavegepant 10 mg	Placebo (653) 10 mg (703)	N/A
Group 2			
202	Zavegepant 10 mg	N/A	603*
Group 3			
106	Zavegepant 100 mg oral	N/A	364

Source: Reviewer created table from data in the SCS.
*This number is inclusive of the 120-day safety update dated July 7, 2022

In the following review, I will summarize the applicant's submitted information and include other analyses that I performed using the data from the Summary of Clinical Safety (SCS), the integrated Summary of Safety (ISS), the 120-day Safety Update Report, and the data sets provided by the applicant.

The primary safety data is from the pooled data from the two pivotal trials (Group 1), with the primary analyses based on Group 1 and Group 3 (open-label, study 202). I focused on Group 1 and Group 3 regarding the review of adverse events. To identify relative differences in risk of 10 mg IN zavegepant, I focused on the controlled studies (Group 1).

Anticipated areas of interest for the safety review

Theoretical safety concerns associated with CGRP inhibition are cardiovascular, cerebrovascular, peripheral vascular, and gastrointestinal. CGRP is a potent vasodilator. In theory, CGRP receptor antagonism during times of ischemia may prevent compensatory vasodilatation from occurring, therefore causing vascular concerns. Hepatotoxicity is another potential safety concern, due to termination of early small molecule CGRP receptor inhibitor development programs due to hepatotoxicity concerns.

Design of open-label, long-term safety study (study 202)

Study 202 was multicenter, long-term, open-label study in patients with migraine. Patients

were to self-administer one dose of zavegepant 10 mg nasal spray up to once a day, as needed, to treat an acute migraine, and up to 8 times per month (28 days).

8.2. Review of the Safety Database

8.2.1. Overall Exposure

At the time of review, a total of 3120 subjects received at least 1 dose of zavegepant (excluding ongoing blinded studies) and 1660 subjects received at least one 10 mg dose of IN zavegepant. This included the 120-day safety update report there were an additional three patients added to study 202, since at the time of filing the submission the case study report had not been finalized. These additional three patients are included in the above totals and in Table 26. In addition, there were 117 patients who were previously enrolled in study 201 who were part of the safety analysis set in study 202.

Table 26 Safety Population, Size, and Denominators for Zavegepant Across Studies

Safety Database for Zavegepant		
Clinical Trial Groups	Zavegepant 10 mg IN	Placebo
Healthy subjects	41	40
Controlled trials*	1038	1090
Uncontrolled trials	657	0
Group 1**	1023	1056
Group 2	603	0
Group 3***	364	0

Source: SCS, Table 2
* Inclusive of zavegepant 10 mg IN dose studies that were double-blinded and placebo-controlled (studies 101, 102, 201 and 301)
**Includes only zavegepant 10 mg IN dose.
***Study 106 which uses zavegepant 100 mg oral dose in healthy subjects.

The Division recommends that long-term safety studies include at least 300 patients treated for at least 6 months and 100 patients treated for at least a year. In addition, as stated in the migraine guidance, these patients should treat on average two migraine attacks per month at minimum. Study 202 meets these criteria (Table 27).

Table 27 Study 202: Patients Who Treated on Average **≥2** Migraine Attacks Per Month Based on Duration of Exposure

	10 mg (n=603)
≥ 3 months	389
≥ 6 months	360

≥ 12 months	298

Source: Study 202 erratum to final CSR, 4.1.6.1A12.

Table 28 shows the number of patients who administered zavegepant 10 mg IN for at least 6 months and at least one year based the average number of administrations per month.

Table 28 Distribution of Patients by Average Number of Exposures Per Month Based on Duration of Treatment

Average exposures per month	At least 6 months exposure	At least one year exposure
≥2	430	326
≥3	399	271
≥4	327	190
≥5	222	106
≥6	144	62
≥7	83	31
≥8	46	13
≥9	23	5
≥10	7	2
≥11	1	0

Source: IR response submitted on August 18, 2022

Reviewer comment: The applicant's proposed dosing regimen for labeling is that zavegepant 10 mg should be administered once in a 24-hour period and that treating more than 8 migraines in a 30-day period has not been established. This descriptions would match the study design of study 202 in that the administration instructions called for only one dose in 24 hours and no more than 8 migraines treated in a month. Table 28 supports the applicant's dose regimen proposal as there are not enough patients to support exposure to zavegepant to greater than 8 times a month but there is an adequate number of patients who average 8 treatments per month for 6 months or greater.

8.2.2. Relevant characteristics of the safety population:

Migraine is more prevalent in woman than men at a ratio of approximately 2:1 or 3:1. In controlled studies (201 and 301) and the open-label study (202) the ratio of women to men is 5:1 in both groups (Table 29 and Table 30). Therefore, the demographic characteristics of the long-term safety Group 1 and 2, are not entirely representative of the intended treatment population. However, there are enough male patients in this open-label trial to provide adequate safety information.

The racial distribution of the study population (Tables 29 and 30) is similar to the U.S. population (https://www.census.gov/quickfacts/fact/table/US/PST045218). The percentage of patients over the age of 65 years is not similar to the U.S. population. The studies did not have a maximum age. The trials did exclude patients with uncontrolled, unstable, or recent cardiovascular disease and patient who had a history of myocardial infarction, acute coronary syndrome, percutaneous coronary intervention, cardiac surgery, stroke, or transient ischemic attack during the 6 months prior to screening. Patients with active hepatic or biliary disorders, a GFR of ≤ 40 ml/min/1.73m^2, BMI ≥35 kg/m^2 (study 201), and BMI ≥40 kg/m^2 (study 301) were also excluded. Therefore, the study populations are likely healthier than the general population and could potentially limit the generalizability of the safety data to patients who would have been excluded in these studies.

Table 29 Group 1: Summary of Demographic Characteristics for the Safety Analysis Set

Demographic Parameters	Placebo (N=1056) n(%)	10 mg (N=1023) n(%)
Sex		
Male	167 (15.8)	180 (17.6)
Female	889 (84.2)	843 (82.4)
Age		
Mean years (SD)	40.4 (12.94)	41.1 (13.10)
Median (years)	39.5	40
Min, max (years)	18, 79	18, 74
Age Group*		
18 to 40	528 (50.0)	491 (48.0)
41 to 64	486 (46.0)	487 (47.6)
65+	42 (4.0)	45 (4.4)
Race		
White	874 (82.8)	812 (79.4)
Black or African American	143 (13.5)	160 (15.6)
Asian	29 (2.7)	34 (3.3)
American Indian or Alaska Native	3 (0.3)	0
Native Hawaiian/ Pacific Islander	1 (< 0.1)	3 (0.3)
Other/Multiple	6 (0.6)	14 (1.4)
Ethnicity		
Hispanic or Latino	227 (21.5)	183 (17.9)
Not Hispanic or Latino	829 (78.5)	840 (82.1)

Body Mass Index (BMI) kg/m²		
Mean (SD)	27.49 (4.849)	27.41 (4.819)
Median	27.35	27.2
Min, Max	15.9, 40.1	15.2, 39.9

Source: SCS, Table 7.

Reviewer comments: Overall there did not appear to be any significant imbalances.

Table 30 Group 2: Summary of Demographic Characteristics for the Safety Analysis Set

Demographic Parameters	10 mg (N=603) n(%)
Sex	
Male	86 (14.3)
Female	517 (85.7)
Age	
Mean years (SD)	42.1 (12.46)
Median (years)	42
Min, max (years)	18, 75
Age Group*	
18 to 40	264 (43.8)
41 to 64	312 (51.7)
65+	27 (4.5)
Race	
White	502 (83.3)
Black or African American	70 (11.6)
Asian	23 (3.8)
American Indian or Alaska Native	2 (0.3)
Native Hawaiian/ Pacific Islander	2 (0.3)
Other/Multiple	4 (0.7)
Ethnicity	
Hispanic or Latino	71 (11.8)
Not Hispanic or Latino	532 (88.2)
Body Mass Index (BMI) kg/m²	
Mean (SD)	26.3 (3.97)
Median	26.5
Min, Max	17, 36

8.2.3. Adequacy of Safety Database

Based on the ICH guidelines for chronic intermittent use medications (1500 overall exposures, at least 300 exposed for 6 months, and 100 exposed for one year), the overall exposure of zavegepant in the safety analysis set is adequate (Table 26 and 27). Given the concern for potential hepatotoxicity with small molecule GCRP receptor inhibitors, the Division had recommend conducting a two- to three-month study with 300 migraine patients or healthy volunteers, using zavegepant on a near daily basis with a comparator arm. Study 106 was conducted to address the hepatotoxicity evaluation with 100 mg oral zavegepant (see section 3.2). The applicant did not use a comparator arm in study 106 and in response to an IR on March 5, 2021, stated that if there were significant events in the 3 times the upper limit of normal (ULN) for AST/ALT or two times the ULN for bilirubin categories, then they would perform another safety study with a placebo arm for comparison. This was found acceptable by the Division. The exposure of the 100 mg oral zavegepant was at least what was achieved by zavegepant 10 mg IN, per the clinical pharmacology review by Dr. Suresh Naraharisetti.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The applicant did identify a programing error for study 202 case study report. The errors were noted as programming errors which affected 13 tables that present eDiary and long-term treatment exposure data (safety analysis set). This did not affect the raw data. The applicant provided updated table to correct data related to the parameter "Time in LTT period category (weeks): n (%)".

The overall submission quality was acceptable with no other specific concerns regarding data quality and integrity.

8.3.2. Categorization of Adverse Events

Adverse Event (AE)

The applicant defined an AE as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject or clinical investigation subject administered an IP and that does not necessarily have a causal relationship with this treatment. An AE could be any unfavorable and unintended sign (including an abnormal laboratory finding for example) symptom, or disease temporally associated with the use of the IP, whether or not considered relate to the IP. AEs can be spontaneously reported or elicited during an open-ended questioning, examination, or evaluation of a subject.

Treatment Emergent Adverse Event

A treatment-emergent adverse event (TEAE) is defined as an event that developed, worsened, or became serious during an on-treatment safety analysis period relative to a pre-treatment safety analysis period. The on-treatment safety analysis period begins with the first dose of the study drug till 7 days after the last dose.

Serious Adverse Event (SAE)

An SAE is any event that meets any of the following criteria at any dose:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received study drug
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are (but not limited to):
    - Intensive treatment in an emergency room or at home for allergic bronchospasm
    - Blood dyscrasias or convulsions that do not result in inpatient hospitalization
    - Development of drug dependency or drug abuse
    - Potential drug induced liver injury
    - Abuse or Overdose of medication

The following hospitalizations are not considered SAEs:

- Emergency room or other hospital department visit <24 hours that does not result in an admission (unless meeting any other SAE criteria)
- Elective surgery planned prior to signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission (i.e., routine colonoscopy)
- Admission encountered for another life circumstance that carries no bearing on health and requires no medical intervention (i.e., lack of housing, care-giver respite, family circumstances)

Process of Recording, Coding, and Categorizing AEs

The collection of non-serious AE information began at the screening visit through the follow up safety visit. Non-serious AEs were followed until conclusion or stabilization or reported as SAEs if they become serious. Follow-up was also required for non-serious AEs that cause interruption or discontinuation of study drug or those that are present at the end of study treatment.

The investigators were to determine the intensity of AEs and the relationship of AEs to study drug. The investigators' terms were coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) available at the start of the study. AEs were to be presented by system organ class and preferred term.

8.3.3. Routine Clinical Tests

Laboratory Testing

For studies 106, 201, 202, 301 the laboratory tests were assessed are in Table 31.

Table 31 Clinical Laboratory Tests

Chemistry	Creatine kinase, sodium, potassium, chloride, bicarbonate, calcium; glucose, hemoglobin A1c (HbA1c), blood urea nitrogen (BUN), serum creatinine, uric acid, lactate dehydrogenase (LDH), total protein, albumin
Hematology	Hemoglobin, hematocrit, red blood cell count (RBCs), white blood cell count (WBCs) with differential, and platelets
Lipid panel	Cholesterol, LDL, HDL, triglycerides
Liver Function Tests (LFTs)	Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and bilirubin (total, direct, indirect)
Urinalysis	pH, specific gravity, ketones, nitrites, urobilinogen, leukocyte esterase, protein, glucose, and blood. If blood, protein or leukocytes are positive, reflex to microscopic examination
Urine drug screen	Screening for drugs of abuse

Source: Reviewer created table

If ALT or AST ≥ 3x ULN OR total bilirubin ≥ 2x ULN at any visit after the baseline visit, the central laboratory performed reflex tests that may have included: CK, GGT, and anti-viral serologies.

In the controlled studies (201 and 301), laboratory testing included hematology, chemistry, lipid panel, urine drug screen, and urinalysis, and occurred at screening and EOT visit.

The open-label study 202, included the same laboratory assessments but on a different schedule since it was a long-term safety study (Table 32).

Table 32 Study 202: Laboratory Assessment Schedule

Procedure	Screening	Pre-Baseline Visit (up to 5 days prior to baseline visit)	Week 2	Week 4	Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 (or EOT)	Week 2 Follow-up Safety Visit

Hematology and Chemistry	X	X		X	X (Weeks 24 and EOT only)	
LFTs	X	X	X	X	X	X
Lipid panel		X			X (Weeks 24 and EOT only)	
Urinalysis		X			X (EOT only)	
Urine Drug Screen for drugs of abuse	X					

Vital Signs
Vital sign measurements included height, weight, body temperature, respiratory rate, sitting blood pressure and sitting heart rate.

For studies 201, 202, and 301, height was measured only at screening. In studies 201 and 301, all other vital signs were taken at screening, baseline, and EOT visits. In study 202, all other vital signs were taken at screening visit, pre-baseline visit, two weeks post-baseline visit, one-month post-baseline visit then monthly, and at the follow-up safety visit.

8.4. Safety Results

8.4.1. Deaths

No deaths were reported in studies 106, 201, 202, and 301.

There was a death of a patient participating in study 302 (b) (4) Study 302 is an ongoing Phase 2/3, double-blind, randomized, placebo-controlled, safety and efficacy dose-ranging study (100 mg or 200 mg oral formulation) of zavegepant administered as an oral soft gelatin capsule for the preventive treatment of migraine.

A 60-year-old male with a history of diverticulitis, lower back pain, and amoxicillin hypersensitivity died due to an SAE of hypertensive cardiovascular disease. The SAE occurred on-treatment, with the patient taking a dose of the blinded study drug on the same day as the SAE. The death certificate was obtained by the applicant. Preliminary data indicated that the subject collapsed while mountain biking. He was reported to have "a heart attack in the middle of the trail" while biking with a group of friends and was pronounced dead at the scene. There were no reports of symptoms prior to the bike ride. The event was considered not related to blinded study drug by the investigator and the applicant.

The patient concomitant medications included fish oil and glucosamine. In addition, he took sumatriptan as his standard of care treatment for migraines, and he took sumatriptan 3-4 days prior to onset of SAE. He did have an elevated blood pressure of 138/98 at screening, and

cardiovascular exam at screening was reported as abnormal for grade 1 systolic murmur that was considered to be not clinically significant but was reported as an AE of mild intensity. The last BP measurement taken at week 8 was 108/83.

The official central read of the electrocardiogram (ECG) at the screening visit was, "Normal ECG, artifact, QT/QTc Unmeasurable/Undeterminable, sinus rhythm, Normal T wave morphology." The unconfirmed ECG machine reading for the same ECG revealed: "Sinus bradycardia (ventricular rate 59 bpm), moderate intraventricular conduction delay (QRS 118 ms), Borderline ECG." The QT/QTcF was 453/451 msec. The ECG was not clinically significant per the principal investigator. The applicant's in-house cardiac electrophysiologist reviewed the subject's ECG tracings retrospectively. The screening tracing found to be "noisy" but revealed sinus bradycardia with a PR interval of 0.20, a normal QRS and a QT interval measured at 440 msec with a sinus rate of 58 bpm for a QTcF of 433 msec. T wave morphology was normal. On a week 4 ECG, a cardiologist read sinus bradycardia at 52 bpm, with atrial and ventricular premature complexes, PR interval of 0.21, normal QRS pattern; T wave morphology was normal. The patient had the AE of bronchitis ongoing at the week 8 visit which was 8 days prior to the SAE. The bronchitis was of mild intensity starting 20 days prior to the SAE. No known COVID-19 test was reported.

The autopsy results were obtained by the applicant. Toxicology results detected caffeine with no other positive findings. SARS-CoV-2 RT-PCR (COVID-19) results were negative. There were two described final diagnoses: 1) hypertensive cardiovascular disease, with cardiac hypertrophy (580 grams), left ventricular hypertrophy (1.7 cm), arteriolonephrosclerosis (slight), aortic atherosclerosis (moderate), and pulmonary edema (right lung 1210 grams, left lung 1480 grams) and 2) nodular prostatic hyperplasia. The autopsy report and death certificate list the cause of death as hypertensive cardiovascular disease and manner of death as natural. An information request to the sponsor to unblind the study drug randomized to the patient was sent. The applicant determined that the patient had been taking 100 mg oral zavegepant.

Reviewer comment: The temporal relationship between administration of the 100 mg oral zavegepant and onset of the SAE is of concern. The patient had also taken sumatriptan 3-4 days prior. The patient was found to have cardiac hypertrophy and atherosclerosis. In addition, there were findings of hypertension in the vital signs. It is difficult to determine definitively whether the death was related to the zavegepant use. Given the theoretical concerns regarding CGRP receptor antagonist and the cardiovascular system and this case, I would recommend pharmacovigilance for myocardial infarction.

8.4.2. Serious Adverse Events

Group 1: Controlled studies (201 and 301) SAEs

The controlled studies (Group 1) had a total of two SAEs reported in patients who received treatment. There was one SAE in a 10 mg zavegepant-treated patient who experienced

thrombosis (narrative below) and one SAE in a placebo-treated patient who experienced a vestibular migraine. There were four patients with five SAEs in patients who were randomized but never received a study drug. Those five SAEs were: clostridium difficile colitis, cholecystitis acute, peritoneal abscess, retroperitoneal abdominal mass, and diverticulum.

Thrombosis

Patient 201-(b) (6)

A 24-year-old female with a history of iron deficiency anemia, and concomitant medications of minerals/vitamins and weekly ethinylestradiol/norelgestromin transdermal patch, experienced a blood clot in one of her legs. Twelve days after administering 10 mg of zavegepant, the patient was involved in a motor vehicle accident in which she was struck from behind by a speeding car and was hospitalized for 3 days. During hospitalization the patient was found to have a blood clot in her leg. During the hospital stay she also experienced AEs of anxiety, back pain, and neck pain, all of which were of moderate intensity. The ethinylestradiol/norelgestromin transdermal patch had been started a little less than 2 months prior to blood clot diagnosis. The thrombosis and AEs were ongoing at time of reporting. The patient did not have a history of smoking.

Reviewer comments: There are multiple confounding factors related to the blood clot. The patient was on a contraceptive and had been involved with a motor vehicle accident just prior to the diagnosis. Although a specific date of the diagnosis was not available, it occurred 12 to 15 days after the single zavegepant administration. Therefore, it is unlikely that this SAE is related to zavegepant.

Group 2: Open-label study (202) SAEs

In the open-label study, out of the 603 patients, there were a total of 9 patients, who after administering at least one dose of 10 mg IN zavegepant, experienced 11 reported SAEs (Table 33). There were no SAEs that occurred more than once. Two of the patients experienced one SAE each (cerebrovascular accident and psychogenic syncope) that were during the follow-up period.

Table 33 Study 202: SAEs

MedDRA System Organ Class Serious Adverse Event (Preferred Term)	10 mg N=603 n(%)
Any SAE	9 (1.2)
Infections and infestations	3 (0.5)
Appendicitis	1 (0.2)
Herpes zoster meningoencephalitis	1 (0.2)

Pneumonia	1 (0.2)
Hepatobiliary disorders	1 (0.2)
Bile duct stenosis	1 (0.2)
Injury, poisoning and procedural complications	2 (0.4)
Concussion	1 (0.2)
Fall	1 (0.2)
Musculoskeletal and connective tissue disorders	1 (0.2)
Back pain	1 (0.2)
Nervous system disorders	2 (0.4)
Cerebrovascular accident	1 (0.2)
Multiple sclerosis	1 (0.2)
Respiratory, thoracic and mediastinal disorders	1 (0.2)
Pleurisy	1 (0.2)
Psychiatric disorders	1 (0.2)
Psychogenic pseudosyncope	1 (0.1)

Source: Study 202 CSR, table 14.3.2.2C and 14.3.2.2D

The following are the narratives for patients who experienced an SAE for group 2 (study 202):

Fall and concussion

Patient 202-(b) (6)

A 51-year-old male with no reported medical history or concomitant medications was hospitalized for a fall and concussion 3 days after a dose of zavegepant. The patient reported that he had tripped and fell down a flight of stairs. Secondary to the fall the patient had AEs of contusion and muscle strain. The applicant was unable to obtain the patient's record despite multiple attempts. The SAE of fall was considered resolved on the day of the incident, and concussion was considered resolved 4 days later after discharge from the hospital. No adjustments were made to zavegepant administration, and the patient continued taking zavegepant and completed the study. The patients had taken 8 doses of zavegepant in the 30 days prior to onset of the SAEs.

Reviewer comments: The SAEs of fall and concussion appear to be secondary to tripping over a flight of stairs. These SAEs are unlikely related to zavegepant.

Psychogenic pseudosyncope

Patient 202-(b) (6)

A 22-year-old female with a history of post-traumatic stress disorder (PTSD), sulfa hypersensitivity, and seasonal allergies experienced the SAE of psychogenic pseudosyncope, 21 days after the last dose of zavegepant and 5 days prior to the patient's follow-up visit. The

patient experienced vasovagal syncope and was hospitalized. In the two days prior to the hospitalization, the patient reported multiple episodes of vasovagal syncope due to anxiety. She was treated with ondansetron 4 mg oral once and IV sodium chloride 500 mL two times. The workup included vital signs, laboratory testing, ECG, echocardiogram, computed tomography (CT) scan of the head without contrast, magnetic resonance imaging (MRI) of the brain without contrast, and an electroencephalogram. All were within normal limits. The patient was discharge 4 days after admission with a home ECG monitoring patch. The patient reported occasional syncopal episodes after discharge. The patient reported that there was no change in her diagnosis and that it was related to stress. No changes were made related to zavegepant. The SAE was considered resolved 6 days after the occurrence.

Reviewer comments: the SAE of psychogenic pseudosyncope was unlikely related to zavegepant based the last dose of zavegepant occurring at least 19 days prior to the onset of symptoms, anxiety, and negative evaluation in the hospital and as an outpatient.

Cerebrovascular accident

Patient 202-(b) (6)

A 28-year-old female with a history of seasonal allergy, dysmenorrhea with no concomitant medications experienced right sided weakness, visual changes, and headache, 8 days after her last dose before the SAE. She was found to have a National Institute of Health Stroke Scale (NIHSS) score of 7 and a CT angiography (CTA) of the head and showed a left posterior cerebral artery (PCA) P2 branch occlusion and the anomalous right vertebral artery entering the transverse foramen at the C3 level. She was also noted to have speech difficulty, right hemianopsia, reduced facial sensation in the distribution of trigeminal V2 and V3, decreased right upper (1/5) and right lower (1/5) extremity strength, and decreased sensation to light touch and pinprick in both the right upper and lower extremities. Vital signs and laboratory tests were unremarkable. COVID-19 polymerase chain reaction (PCR) test was negative, partial thromboplastin time (PTT) and prothrombin time (PT) were within normal limits, lupus anticoagulant was not detected, anticardiolipin antibody IgM and IgG was negative, and beta 2 glycoprotein 1 antibody IgM and IgG were negative . CT brain perfusion scan showed a left occipital lobe 20 mL ischemic penumbra without cortical infarct; CT of the head without contrast revealed no acute intracranial abnormality.

A rapid diffusion study was performed which confirmed an area of reversible ischemia without any evidence of infarct. The subject was considered not a good candidate for thrombectomy due to unfavorable vascular anatomy that limited access to the occluded artery. The subject was felt to be a good thrombolytic candidate and was given intravenous tissue plasminogen activator (TPA). Her symptoms largely resolved with a NIHSS of 0 two days after hospitalization. The patient was diagnosed with a cerebrovascular accident due to thrombosis of the left PCA.

A day after admission, a brain MRI without contrast showed an acute left thalamic infarct with no additional areas of restricted diffusion, no acute hemorrhage, a few scattered nonspecific

foci of T2 hyperintensity in the cerebral white matter that were potentially early findings of chronic ischemia. MRA demonstrated interval recanalization of the P2 segment left PCA from CTA a day earlier. Cardiac MRI with and without contrast revealed no intracavitary or enhancing cardiac mass, small defect within the interatrial septum with a differential diagnosis of a patent foramen ovale (PFO), and LV ejection fraction of 55%. Two weeks later a cardiologist recommend closure of the PFO with the procedure taking place 29 days after SAE onset.

A hypercoagulability panel showed: negative Factor V Leiden, mixed picture for antiphospholipid syndrome, lupus anticoagulant positive, anticardiolipin antibodies IgA, IgG, and IgM were negative, ANA positive at 1:80 with a speckled appearance, dilute Russell Viper Venom Test was weakly positive, and complement levels (C3, C4) were normal. This test was done after the initial laboratory assessment noted earlier.

The subject had no history of early pregnancy loss, venous thromboembolism, heart disease, or any cardiac risk factors. Hospital records describe recent pregnancy. She denied use oral contraceptives, or regular smoking. The patient had taken a total of 3 doses of zavegepant prior to onset of SAE in the 30 days before. Zavegepant was discontinued due to the SAE and the subject withdrawn from the study.

Eleven days prior to the SAE the patient experience AEs of chest discomfort, headache, and oropharyngeal pain which were considered resolved 3 days later. The patient did miss a week 12 visit, 7 days after the onset of those AEs due to "COVID symptoms" although a rapid COVID test was negative around 7 days prior. The investigator assessed that these AEs were not related to the SAE and the zavegepant was not related to the SAE.

Reviewer comment: The patient did not have any identified risks factors in her medical history. The PFO discovered on evaluation could be related to the stroke as patients with a PFO have an increased risk for stroke. There is a concern for potential CGRP inhibition affected cardiovascular or cerebrovascular system because CGRP is a potent vasodilator. Zavegepant's half-life is around 6.6 hours. Zavegepant is less likely to be related given the time of onset was 8 days after the last dose however it cannot be ruled out completely.

Pneumonia and pleurisy

Patient 202-(b) (6)

56-year-old female with a history of constipation, anxiety, depression, amoxicillin hypersensitivity, insomnia, seasonal allergy, and hypothyroidism presented to the emergency department (ED) with symptoms of sharp right sided chest wall pain that was worse with movement and breathing. The last dose of zavegepant was 2 days prior to onset of SAEs. Laboratory results demonstrated elevate WBC and neutrophils, and chest x-ray was negative for acute intrathoracic process. Three days later the patient's physician prescribed azithromycin. Ten days after onset of symptoms the patient returned to her physician and was prescribed levofloxacin and prednisone. A chest x-ray was also done demonstrated a right

upper lobe pneumonia. The patient was seen 16 days after onset and was sent to the ED due to worsening of symptoms with elevated WBC. The patient was treated with IV antibiotics and prednisone. The patient responded well and was discharged 2 days after admission. The patient was reported to have experienced the SAEs of right upper lobe pneumonia and pleurisy. No action was taken regarding zavegepant and SAEs were resolved 46 days after onset.

Reviewer comments: It is not clear the cause of pneumonia and pleurisy. There is a temporal relationship between this SAE and the use of zavegepant. Given the continued use of zavegepant without return of symptoms I think it is unlikely that these SAEs are related to zavegepant. In addition, I think that it would be more likely that the pneumonia would be community acquired and mechanistically would be unlikely related to zavegepant administration.

Appendicitis

Patient 202-(b) (6)

32-year-old female with a history of nasal polyps, pain in extremity, iron deficiency, and seasonal allergy presented to the ED with severe right lower quadrant abdominal pain and tenderness. The last dose of zavegepant was taken the day before. The patient was found to have an elevated WBC, and low hemoglobin/hematocrit. CT scan demonstrated finding concerning for appendicitis, and a right adnexal complex cystic and solid appearing mass. The patient also had AEs of insomnia, hyponatremia, abdominal pain lower, adnexal uteri mass, and sepsis. Laparoscopic appendectomy with drainage of an ovarian cyst was performed the next day. At that time the SAE was considered resolved. The patient was discharged two days after admission. No action was taken in regard to zavegepant administration as the result of the appendicitis.

Reviewer comment: Appendicitis is not considered a rare condition and in an open-label study it is difficult to conclude that this SAE was related to zavegepant.

Multiple sclerosis

Patient 202-(b) (6)

A 33 -year-old female with a history of anxiety and depression, presented with right-sided numbness that had been progressive for approximately 9 months prior. It had initially started in her right chest and progressed down to her right foot, along with weakness and leg shakiness when trying to raise her leg. A neurological examination revealed right-sided numbness from the right nipple down to the leg, with weakness in the right lower leg. Chest x-ray, CBC, and comprehensive metabolic panel were unremarkable. Findings on an MRI of the brain with and without contrast were suggestive of demyelinating disease. MRI of the cervical, and thoracic spine demonstrated extensive demyelinating lesions. The lumbar spine was notable for subtle abnormal cord signal of the conus medullaris, suggestive of chronic demyelinating plaques in the setting of multiple sclerosis. The patient was discharged 2 days after admission.

In the 30 days prior to the SAE, the patient took 5 doses of zavegepant with the last dose 6 days before presenting to the hospital. The patient received the first dose around 11 months prior to presentation to the hospital.

Reviewer comment: It is unlikely that the SAE of multiple sclerosis is related to zavegepant based on the mechanism of action.

Back pain

Patient 202-(b) (6)

A 65-year-old female with a history of attention deficit hyperactivity disorder (ADHD), osteoporosis, and anxiety, presented with intractable back pain requiring hospitalization. The patient had back pain for the 6 days prior due to osteoporosis. The last dose of zavegepant taken prior to hospitalization was 14 days prior. During hospitalization an MRI of the lumbar spine showed multilevel spondylitis and degenerative changes, and prominent left extraforaminal disc profusion impinging the left L1 nerve root. The patient received a left L2-L3 interlaminar epidural injection of methylprednisolone with improvement of symptoms. The patient was discharged 4 days after admission but hospitalized 10 days after first admission due to continued symptoms and discharged the next day with a lidocaine patch. The SAE was considered resolved 24 days after initial admission hospital. No changes were made to zavegepant, and the patient completed the study.

Reviewer comment: Zavegepant is unlikely to be related to back pain given the evidence and history of osteoporosis.

Herpes zoster meningoencephalitis

Patient 202-(b) (6)

A 36-year-old female with a history of asthma, and depression, reported symptoms of severe headaches, pain, and bone aches. The patient eventually presented to the ED with severe intractable headache, neck pain, stiffness, eye pain, photophobia, and right-sided rash on her abdomen and flank. The patient was diagnosed with herpes zoster meningoencephalitis after workup. The patient was treated with IV acyclovir with improvement in symptoms and rash. Patient was discharged 3 days after admission but returned to the ED the next day with persistent headache, neck pain, and nausea. After further evaluation the SAE was considered resolved 3 days after admission.

The last dose of zavegepant was taken on the same day as onset of symptoms. The subject was withdrawn from the study.

Reviewer comment: Given the mechanism of action of zavegepant, herpes zoster viral meningitis is not likely to be related to zavegepant administration.

Bile duct stenosis

A 52-year-old female with a history of phenobarbital hypersensitivity presented to the ED with abdominal pain radiating to her chest that was worse with eating. The patient presented to the ED two days after the last dose of zavegepant. Her first dose of zavegepant was 12 days prior to presentation to the ED. The patient had a 4-to-6-week history of the pain and losing 15 to 17 lbs. Three week prior to presentation she had a magnetic resonance cholangiopancreatography (MRCP) and was referred for an outpatient endoscopic retrograde cholangiopancreatography (ERCP). She was hospitalized for a common bile stricture which was reported as an SAE of bile duct stenosis. The next day she was discharged and told to follow up with a gastroenterologist for an ERCP. The patient reported 50 days after hospitalization that her symptoms had resolved. Zavegepant was discontinued due to the SAE, and she was withdrawn from the study.

Reviewer comment: Symptoms had started prior to first zavegepant use, therefore I do not think this SAE is related to zavegepant.

Group 3 SAEs: Study 106
There were no SAEs in study 106.

Group 4 SAEs: Study 101 and 102 (Phase 1 SAD and MAD studies)
There were no reported SAEs in studies 101 and 102

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In Group 1 (studies 201 and 301), there were no AEs leading to treatment discontinuation. In Group 2 (study 202), there were 45 patients (7.5%) out of 603 patients had AE leading to discontinuation (Table 34). The most frequent AEs leading to study drug discontinuation were dysgeusia (9 [1.5%]), nasal discomfort (5 [0.8%]), AST increase (5 [0.8%]), ALT increase (4 [0.7%]), throat irritation (4 [0.7%]), dizziness (3 [0.5%]), migraine (3 [0.5%]), rhinorrhea (3 [0.5%]), and nausea (3 [0.5%]).

Table 34 Open-label Study (202): All Adverse Events Leading to Discontinuations

MedDRA System Organ Class Serious Adverse Event (Preferred Term)	10 mg N=603 n(%)
Any AE	45 (7.5)
Nervous system disorders	18 (3.0)
Dysgeusia	9 (1.5)
Dizziness	3 (0.5)
Migraine	3 (0.5)
Cerebrovascular accident	1 (0.2)
Disturbance in attention	1 (0.2)

Neuropathy peripheral	1 (0.2)
Sedation	1 (0.2)
Taste disorder	1 (0.2)
Respiratory, thoracic, and mediastinal	11 (1.8)
Nasal discomfort	5 (0.8)
Throat irritation	4 (0.7)
Rhinorrhea	3 (0.5)
Asthma	1 (0.2)
Epistaxis	1 (0.2)
Nasal congestion	1 (0.2)
Nasal mucosal disorder	1 (0.2)
Rhinalgia	1 (0.2)
Gastrointestinal disorders	5 (0.8)
Nausea	3 (0.5)
Vomiting	2 (0.3)
Esophagitis	1 (0.2)
Investigations	5 (0.8)
Aspartate aminotransferase increased	5 (0.8)
Alanine aminotransferase increased	4 (0.7)
Blood alkaline phosphatase increased	1 (0.2)
Blood creatine phosphokinase increased	1 (0.2)
Blood lactate dehydrogenase increased	1 (0.2)
Gamma-glutamyltransferase increased	1 (0.2)
Infections and infestations	4 (0.7)
COVID-19	2 (0.3)
Herpes zoster meningoencephalitis	1 (0.2)
Sinusitis	1 (0.2)
Musculoskeletal and connective tissue disorders	3 (0.5)
Arthralgia	1 (0.2)
Muscular weakness	1 (0.2)
Rheumatoid arthritis	1 (0.2)
Cardiac disorders	2 (0.3)
Atrial fibrillation	1 (0.2)
Wolff-Parkinson-White syndrome	1 (0.2)
Eye disorders	2 (0.3)
Eyelid irritation	1 (0.2)
Scleral hyperemia	1 (0.2)
General disorders and administration site conditions	2 (0.3)

Facial pain	1 (0.2)
Fatigue	1 (0.2)
Psychiatric disorders	2 (0.3)
Anxiety	2 (0.3)
Hepatobiliary disorders	1 (0.2)
Bile duct stenosis	1 (0.2)
Injury, poisoning and procedural complications	1 (0.2)
Procedural pain	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.2)
Acoustic neuroma	1 (0.2)
Vascular disorders	1 (0.2)
Hypertension	1 (0.2)

Source: Study 202, table 14.3.2.3A.

8.4.4. Significant Adverse Events

The applicant defined severity categories by the following, which applied to AEs and SAEs:

- Mild: Is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: Is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
- Severe: Interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention.

The majority of AEs were of mild intensity for both the controlled studies and open-label study.

Table 35 Controlled Studies: TEAEs by Intensity

	Placebo N=225 n(%)	Zavegepant 10 mg N=432 n(%)
Mild	172 (76.4)	307 (71.1)
Moderate	47 (20.1)	115 (26.6)
Severe	6 (2.7)	10 (2.3)

Source: Reviewer created from ISS dataset ADAE where TRTEMFL=Y, STUDYID=BHV3500-201 or BHV3500-301, TRTA=10 MG or PLACEBO

Table 36 Controlled Studies: Patients with TEAEs by Intensity

	Placebo	Zavegepant 10 mg

	(N=1056) n(%)	(N=1023) n(%)
Mild	134 (12.7)	217 (21.2)
Moderate	37 (3.5)	85 (8.3)
Severe	4 (0.4)	9 (0.9)

Source: OCS Analysis Studio, Custom Table Tool. Columns - Dataset: Demographics; Filter: SAFFL = 'Y', TRT01A = 'Zavegepant 10 mg' or 'Placebo', STUDYID = 'BHV3500-201' or 'BHV3500-301'. Table Section 1 - Dataset: Adverse Events; Filter: AESEV = 'MILD' or 'MODERATE' or 'SEVERE', SAFFL = 'Y', STUDYID = 'BHV3500-201' or 'BHV3500-301', TRTEMFL = 'Y'

Table 37 Open-label Study: TEAEs by Intensity

	Zavegepant 10 mg (N=1920) n(%)
Mild	1350 (70.2)
Moderate	542 (27.3)
Severe	28 (1.5)

Source: Reviewer created from 120-day SUR dataset ADAE where TRTEMFL=Y,

Table 38 Open-label Study: Patients with TEAEs by Intensity

	Zavegepant 10 mg (N=603) n(%)
Mild	378 (38.8)
Moderate	233 (23.9)
Severe	22 (3.6)

Source: OCS Analysis Studio, Custom Table Tool. Columns - Dataset: Demographics; Filter: STUDYID = 'BHV3500-202'. Adverse Events; Filter: STUDYID = 'BHV3500-202', TRTEMFL = 'Y', SAFFL = 'Y'.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The most common TEAEs in the controlled studies, occurring ≥1% of 10 mg zavegepant-treated patients, were taste disorder, nausea, nasal discomfort, vomiting, throat irritation, fatigue/somnolence (Table 39). Of these TEAEs only fatigue, somnolence and nasal congestion were similar in both placebo and the zavegepant groups. I evaluated all TEAEs to identify any TEAE that had a higher incidence in the zavegepant group than placebo by at least 0.5%. Other than the first four TEAEs in Table 39, there were no other TEAEs that met those criteria. Of the TEAEs that occurred in ≥2% of zavegepant patients and that occurred ≥1% more than placebo, there are three. They were TEAEs of taste disorder, nausea, nasal discomfort, and vomiting (when rounded to nearest percentage). For the TEAE of taste disorder I combine taste disorder,

Table 39 Controlled Studies: TEAEs occurring **≥1%** of Zavegepant-Treated Patients and Greater than Placebo-Treated Patients

Preferred Term	Placebo (N=1056) n(%)	Zavegepant 10mg (N=1023) n(%)	Risk Difference Rounded (%)
Taste disorder*	46 (4.4)	184 (18.0)	14
Nausea	9 (0.9)	36 (3.5)	3
Nasal discomfort	8 (0.8)	27 (2.6)	2
Vomiting	3 (0.3)	16 (1.6)	1
Throat irritation	1 (0.1)	12 (1.2)	1
Nasal congestion**	10 (0.9)	12 (1.2)	0
Fatigue, somnolence***	10 (0.9)	11 (1.1)	0

Source: OCS Analysis Studio, Safety Explorer. Filters: TRT01A = "Placebo" and STUDYID = "BHV3500-201" or "BHV3500-301" and SAFFL = "Y" (Placebo); TRT01A = "Zavegepant 10 mg" and STUDYID = "BHV3500-201" or "BHV3500-301" and SAFFL = "Y" (Zavegepant 10 mg); TRTEMFL = "Y" (Adverse Events).
*Taste disorder includes tastes disorder, dysgeusia, and ageusia
**Nasal congestion includes nasal congestion, rhinitis, nasal edema, and nasal inflammation
***Fatigue, somnolence includes fatigue and somnolence

Reviewer comment: The applicant has proposed including dysgeusia, nausea, and nasal discomfort in the PI, since those TEAEs occurred in in ≥2% of zavegepant patients and that occurred ≥1% more than placebo. I recommend that the numbers be appropriately updated to combine of dysgeusia and ageusia with taste disorder. I also recommend that vomiting be included in the table given that it could be rounded to 2% and that there is a notable difference between zavegepant and placebo in occurrence.

Table 40 Group 2: TEAEs in Study 202 occurring **≥2%** of Zavegepant-Treated Patients

Preferred Term	Zavegepant 10 mg (N=603) n(%)
Taste disorder*	250 (41.5)
Nasal discomfort	66 (10.9)
Covid-19	45 (7.5)
Nasal congestion**	41 (6.8)
Nausea	37 (6.1)

Throat irritation	33 (5.5)
Back pain	32 (5.3)
Pyrexia	22 (3.6)
Myalgia	21 (3.5)
Rhinorrhea	21 (3.5)
Arthralgia	20 (3.3)
Abnormal LFT***	19 (3.2)
Abdominal pain, dyspepsia****	18 (3.0)
Oropharyngeal discomfort	18 (3.0)
Somnolence, fatigue*****	18 (3.0)
Insomnia	16 (2.7)
Pain in extremity	16 (2.7)
Vomiting	16 (2.7)
Sneezing	15 (2.5)
Epistaxis	14 (2.3)
Upper respiratory tract infection******	14 (2.3)
Cough	13 (2.2)
Urinary tract infection	13 (2.2)
Sinusitis	12 (2.0)

Source: OCS Analysis Studio, Safety Explorer. Filters: TRT01A = "Zavegepant" and SAFFL = "Y" (Zavegepant); TRTEMFL = "Y" (Adverse Events). Percent Threshold: Zavegepant ≥ 2%.
*Taste disorder also includes dysgeusia, and ageusia
**Nasal congestion also includes rhinitis, nasal edema, nasal inflammation, rhinitis allergic
***Abnormal LFT includes alanine aminotransferase increased, aspartate aminotransferase increased, liver function test increased, transaminases increased
****Abdominal pain, dyspepsia includes dyspepsia, abdominal pain, abdominal discomfort, abdominal pain lower, and abdominal pain upper
*****Somnolence, fatigue includes fatigue and somnolence
******Upper respiratory tract infection also includes viral upper respiratory tract infection

Reviewer comment: Overall the TEAE profile in the open label study appears similar to the controlled studies. No new safety signals were identified.

8.4.6. Laboratory Findings

For the controlled studies, I reviewed the mean change from baseline as well as the worst abnormalities during the treatment period for hematology, chemistry, and urinalysis results. There were no clinical meaningful imbalances noted except for the mean change from baseline for creatine kinase (Table 41).

Table 41 Controlled Studies: CK Change from Baseline

CK (U/L)	Placebo N=1040	Zavegepant 10 mg N=997
Baseline		
Mean (SD)	105.1 (95.35)	103.2 (77.13)
Median	80.0	81.0
Min, Max	12, 1115	15, 837
End of Treatment		
Mean (SD)	113.6 (133.40)	122.7 (230.92)
Median	79.0	82.0
Min, Max	15, 2396	18, 4967
Change from baseline		
Mean (SD)	7.8 (122.47)	19.8 (227.14)
Median	2.0	1.0
Min, Max	-979, 2316	-532, 4848

Source: ISS, Appendix 3.3.1B

The applicant utilized the Common Terminology Criteria for Adverse Events (CTCAE) scale, version 5.0, for grading laboratory data. Based on that scale CK toxicity is graded as the following:

> CK CTCAE Grading:
> Grade 1: >upper limit of normal (ULN) up to 2.5xULN
> Grade 2: ≥2.5xULN up to 5xULN
> Grade 3: >5xULN up to 10xULN
> Grade 4: >10xULN

Table 42 shows the worst grade regarding CK, after treatment started during the study. There was no notable imbalance.

Table 42 Controlled Studies: Worst CK Elevations During Treatment

CK	Placebo N=1044 n(%)	Zavegepant 10 mg N=1000 n(%)
Grade 1 or 2	131 (12.5)	133 (13.3)
Grade 3	6 (0.6)	3 (0.3)
Grade 4	3 (0.3)	5 (0.5)

Source: ISS, appendix 3.1.1.1

Reviewer comment: Table 42 did not demonstrate a notable imbalance between zavegepant-treated patients and placebo-treated patients grading the grades of CK elevations. In addition, there were no AEs of "myopathy" in the controlled studies.

Investigation-Related AEs

Investigation-related AEs in the controlled studies were low, and overall well-balanced. There was a small higher incidence of creatine phosphokinase increase (0.7%) versus placebo (0.4%).

Table 43 Controlled Studies: Investigation-Related AEs

Preferred Term	Placebo (N=1056) n(%)	Zavegepant 10 mg (N=1023) n(%)
Alkaline phosphatase	0 (0)	1 (0.1)
Alkaline phosphatase increased	0 (0)	1 (0.1)
ALT increased	1 (0.1)	1 (0.1)
AST increased	1 (0.1)	0 (0)
Bilirubin increased	1 (0.1)	0 (0)
Creatine phosphokinase increased*	4 (0.4)	7 (0.7)
Creatinine increased	0 (0)	1 (0.1)
Lactate dehydrogenase increased	0 (0)	1 (0.1)
Potassium increased	1 (0.1)	0 (0)
Uric acid increased	2 (0.2)	0 (0)
Urine present	0 (0)	2 (0.2)
CSF specific gravity decreased	1 (0.1)	0 (0)
Glomerular filtration rate decreased	0 (0)	2 (0.2)
Hematocrit decreased	1 (0.1)	0 (0)
Hemoglobin decreased	1 (0.1)	0 (0)
Hepatic enzyme increased	0 (0)	1 (0.1)
Liver function test increased	3 (0.3)	0 (0)
Lymphocyte count increased	1 (0.1)	0 (0)
Monocyte count increased	1 (0.1)	0 (0)
Neutrophil count increased	1 (0.1)	0 (0)
Platelet count decreased	1 (0.1)	0 (0)
Protein urine present	0 (0)	1 (0.1)
Specific gravity urine decreased	1 (0.1)	0 (0)
Urine ketone body present	0 (0)	1 (0.1)
White blood cell count increased	1 (0.1)	0 (0)
White blood cells urine positive	0 (0)	2 (0.2)

Source: OCS Analysis Studio, Safety Explorer. Filters: TRT01A = "Placebo" and STUDYID = "BHV3500-201" or "BHV3500-301" and SAFFL = "Y" (Placebo); TRT01A = "Zavegepant 10 mg" and STUDYID = "BHV3500-201" or "BHV3500-301" and SAFFL = "Y" (Zavegepant 10 mg); TRTEMFL = "Y" and AEBODSYS = "Investigations" (Adverse Events).
*Creatine phosphokinase increase also includes creatine phosphokinase

8.4.7. Vital Signs

Vital sign measurements included height, weight, body temperature, respiratory rate, sitting blood pressure and sitting heart rate (see section 8.3.3 for schedule of assessment).

Controlled Studies Vital Sign Assessment
For the controlled studies, there were no clinically meaningful mean or median changes from baseline for any of the vital signs and the noted changes were all similar between the zavegepant 10 mg group and the placebo group when reviewing study 201 CSR (Table 14.3.5.1A) and study 301 CSR (Table 14.3.5.1A). The applicant provided vital sign and physical measurement abnormalities that occurred after taking a dose of the study drug till 7 days after their last dose (Table 44). There do not appear to be imbalances for the SBP, DBP, and HR abnormalities.

Table 44 Controlled Studies: Vital Sign Abnormalities Safety Analysis Set

	Placebo N=1045 n(%)	10 mg N=1003 n(%)
SBP (mmHg)		
<90	6 (0.6)	5 (0.5)
>140	42 (4.0)	35 (3.5)
>160	2 (0.2)	0
DBP (mmHg)		
<90	1 (<0.1)	1 (<0.1)
>140	48 (4.6)	52 (5.2)
>160	2 (0.2)	2 (0.2)
HR (bpm)		
<60	53 (5.1)	53 (5.3)
>100	13 (1.2)	5 (0.5)

Source: SCS, Table 25

Open-label Study and Hepatotoxicity Study Vital Sign Assessment
The applicant provided vital sign abnormalities of the safety analysis set (Table 45 and 46).

Table 45 Open-label: Vital Sign Abnormalities Safety Analysis Set

	10 mg N=581 n(%)
SBP (mmHg)	
<90	20 (3.4)
>140	88 (15.1)
>160	2 (0.3)
DBP (mmHg)	
<90	12 (2.1)
>140	120 (20.7)
>160	6 (1.0)
HR (bpm)	
<60	113 (19.4)
>100	24 (4.1)

Source: Study 202 CSR, Table 12-9

Hepatotoxicity Study (302): Vital Sign Assessment

Table 46 Group 3: Vital Sign Abnormalities Safety Analysis Set

	Zavegepant 100 mg oral N=360 n(%)
SBP (mmHg)	
<90	0
>140	45 (12.5)
>160	3 (0.8)
DBP (mmHg)	
<90	2 (0.6)
>140	35 (9.7)
>160	1 (0.3)
HR (bpm)	
<60	79 (21.9)
>100	2 (0.6)

Source: SCS, Table 27

Reviewer comment: Both the open-label study and the hepatotoxicity study demonstrate a higher percentage of SBP and DBP elevation than in the controlled studies. However, given that there is no comparator group, it is difficult to draw conclusions.

Study 101 and Study 102: Single and Multiple Dose Studies

Study 101 was a double-blind placebo controlled, randomized, single ascending dose study. There were 9 dose regimens to be administered intranasally (0.1 mg, 0.3 mg, 1 mg, 3 mg, 5 mg, 10 mg, 20 mg, 20 mg [2 x 10 mg], and 40 mg [2 x 20 mg]).

Table 47 Study 101: Mean Change from Baseline SBP (mmHg)

Postdose Time (hrs)	Placebo (N-18)	5 mg (N=6)	10 mg (N=6)	20 mg (N=6)	20 mg (2 x 10 mg) (N=6)	40 mg (2 x 20 mg) (N=6)
1	1.3	-2.0	4.5	1.2	0.8	8.0
1.5	2.1	0	2.8	1.2	5.2	4.5
2	1.3	-5.2	2.8	0.2	-1.7	6.7
2.5	1.5	-3.0	1.8	-1.3	-2.0	5.0
3	1.1	-3.2	0.0	0.5	-0.8	6.8
4	0.5	-0.8	2.0	-1.8	-4.7	15.3
6	0.8	-6.3	2.0	0.3	0.5	-1.5
8	-2.8	-6.8	-4.3	-0.3	-4.2	-3.8

Source: Study 101 CSR, Table 14.3.5A

Table 48 Study 101: Mean Change from Baseline DBP (mmHg)

Postdose Time (hrs)	Placebo (N-18)	5 mg (N=6)	10 mg (N=6)	20 mg (N=6)	20 mg (2 x 10 mg) (N=6)	40 mg (2 x 20 mg) (N=6)
1	1.1	-0.3	3.2	0.8	0.2	4.5
1.5	0.4	-1.5	0.7	2.0	2.5	4.7
2	0	-2.3	0.5	2.2	-0.7	3.0
2.5	-0.9	-1.7	0.2	-0.2	-2.2	4.7
3	-0.4	-2.0	0.7	0.5	-1.3	2.2
4	0.1	-1.5	3.0	-0.7	2.0	7.2
6	-2.1	-5.8	1.2	-1.5	-1.0	-1.7
8	-4.3	-7.2	-6.3	-0.7	-5.8	-1.8

Source: Study 101 CSR, Table 14.3.5A

Reviewer comment: The median T_{max} was between 0.5 and 1 hours in this study. There does not appear to be a clear pattern for the mean changes from baseline SBP and DBP except at the 40 mg dose, where there was a consistently higher increase in SBP and DBP from 1-hour postdose to 4 hours postdose versus placebo. However, this dose is 4 times the proposed marketed dose.

Study 102 was a double-blind, placebo controlled, randomized, multiple ascending dose study. There were 4 dose cohorts (Table 49) that were to receive daily dosing for 14 days.

Table 49 Study 102 Cohorts

Cohort	Planned Dose Level of BHV-3500
1	5 mg or matching placebo (alternate nostril each day)
2	10 mg or matching placebo (alternate nostril each day)
3	20 mg or matching placebo (alternate nostril each day)
4	10 mg or matching placebo, with a two-hour interval prior to repeat spray of 10 mg or matching placebo in the alternate nostril, each day or 20 mg or matching placebo, with a two-hour interval prior to repeat spray of 20 mg or matching placebo in the alternate nostril, each day.

Source: Study 102 protocol, Table 3

Table 50 Study 102: Mean Change from Baseline SBP (mmHg) on Day 14

Postdose Time (hrs)	Placebo (N-16)	5 mg (N=9)	10 mg (N=9)	20 mg (N=9)
1	-10.0	-11.6	-8.6	-6.9
2	-8.4	-9.0	-12.8	-3.4
4	-10.3	-11.3	-13.3	-4.9
6	-10.1	-10.1	-8.9	0.9
8	-12.2	-4.3	-11.7	-3.4
12	-9.1	-9.1	-8.2	-1.6

Source: Study 102 CSR, Table 14.3.5A

Table 51 Study 102: Mean Change from Baseline DBP (mmHg) on Day 14

Postdose Time (hrs)	Placebo (N-16)	5 mg (N=9)	10 mg (N=9)	20 mg (N=9)
1	-8.6	-14.8	-10.2	-8.8
2	-8.7	-13.9	-12.9	-7.8
4	-8.9	-15.4	-13.0	-9.7
6	-9.0	-14.1	-12.2	-6.2
8	-10.6	-14.5	-13.7	-8.1
12	-8.6	-15.3	-12.1	-8.2

Source: Study 102 CSR, Table 14.3.5A

Reviewer comment: In reviewing the SBP and DBP on day 14, there is no notable pattern of higher blood pressure with use of zavegepant versus placebo.

8.4.8. Electrocardiograms (ECGs)

For the studies 201 and 301, I reviewed the change from baseline of the safety analysis set for ventricular rate, PR interval, QRS interval, QTcB interval, and QTcF interval by reviewing table 14.3.5.2A in both studies' CSRs. I did not identify any clinically meaningful imbalance between zavegepant 10 mg and placebo groups. There was no clinically meaningful difference between the zavegepant 10 mg and placebo groups in the incidence of ECG abnormalities (Table 52).

Table 52 Controlled Studies (201 and 301): On-treatment QTcB and QTcF Abnormalities Post-Baseline

	Placebo N=1023 n(%)	Zavegepant 10 mg N=971 n(%)
QTcB (msec)		
> 450	141 (13.8)	145 (14.9)
> 480	8 (0.8)	6 (0.6)
> 500	0	2 (0.2)
QTcF (msec)		
> 450	35 (3.4)	36 (3.7)
> 480	0	1 (0.1)
> 500	0	0

Source: SCS, Table 25

In the open-label long-term safety study (study 202) no patient had a QTcF >500 (Table 53).

Table 53 Open-label Study: On-treatment ECG Abnormalities

	Zavegepant 10 mg N=543 n(%)
QTcB (msec)	
> 450	95 (17.5)
> 480	2 (0.4)
> 500	0
QTcF (msec)	
> 450	35 (6.4)
> 480	0
> 500	0

Source: SCS, Table 26

ECG-Related TEAEs

For the controlled studies, there were two ECG-related TEAEs of ECG QT prolonged in the 10 mg zavegepant population and none in the placebo population. In the open-label long-term safety study, there were two patients with different ECG-related TEAE. One patient experienced a mild TEAE of ECG QT prolonged and the other patient was reported to have moderate TEAEs of ECG T wave abnormal and ECG abnormal.

8.4.9. QT

The applicant conducted individual and pooled cQT analysis of SAD and MAD studies (BHV3500-101 and BHV3500-102) which was reviewed by the Interdisciplinary Team for QT Studies (QT-IRT). The QT-IRT reviewed the Phase 1 SAD (study 101) and MAD (study 102) studies and did not detect a significant QTcF prolongation effect of zavegepant. The review noted that the highest dose evaluated was 40 mg (20 mg x 2 sprays) IN which was around a 4-fold margin over the maximum therapeutic exposures (Cmax:~13.4 ng/mL) associated with the proposed dosing regimen. They note that this covers two times the worst-case exposure scenario (in moderate hepatic impairment and subjects on concomitant administration with OATP1B3 and NTCP inhibitors). The findings are further supported by nonclinical data showing a low risk for QT prolongation by direct inhibition of the hERG current at therapeutic exposure. QT-IRT has proposed the following language be included in the PI: "At a dose 4 times the maximum approved recommended daily dose, <Tradename> does not prolong the QT interval to any clinically relevant extent." Please see Dr. Anantha Ram Nookala's review, from August 3, 2022.

8.4.10. Immunogenicity

N/A

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Cardiovascular, Cerebrovascular, and Peripheral Vascular Disease

There is a theoretical cardiovascular safety risk due to the role of CGRP as a potent vasodilator. In particular, in the setting of ischemia there is a theoretical concern that inhibiting CGRP would lead to a lack of compensatory vasodilation. CGRP receptors are located in the central and peripheral nervous system, as well as the cardiovascular system (Edvinsson et al 2019).

Studies have associated migraine and specifically migraine patients with aura with increased risk of vascular disease (Adelborg et al, 2020). There has been some evidence that migraine patients are at an increased risk of stroke and cardiovascular events (Li et al, 2015).

Reviewer comment: Previous CGRP receptor antagonists applications prompted consideration to include a warning for the theoretical cardiovascular safety risk in patients with major cardiovascular disease. The Division of Cardiovascular and Renal Products (DCRP) concluded in their review that there is a consensus opinion that CGRP is one of multiple redundant mechanisms regulated blood flow. In addition, the Medical Policy and Program Review Council

(MPPRC) reviewed the animal data and felt that this data did not support including a warning in section 5 of the PI.

The prevalence of cardiovascular risk factors was low in the controlled studies (201 and 301), and the open-label study (202). The applicant identified cardiovascular risk factors that would contraindicate triptan use as well as general risks factors for cardiovascular disease (Table 54 and 55). Ischemic coronary artery disease includes angina pectoris, myocardial infarction, acute coronary syndrome, documented silent ischemia, percutaneous coronary intervention, stent placement, and coronary artery bypass surgery.

Table 54 Controlled Studies: Baseline Cardiovascular Risk Factors

	Placebo N=1056 n(%)	Zavegepant 10 mg N=1023 n(%)
Cardiovascular risk factors contraindicating triptans		
Ischemic coronary artery disease	0	3 (0.3)
Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders arrhythmias	1 (<0.1)	0
History of stroke or transient ischemic attack	1 (<0.1)	4 (0.4)
Peripheral vascular disease	1 (<0.1)	0
Ischemic bowel disease	0	0
Uncontrolled hypertension	0	0
General risk factors		
Family history of coronary artery disease	131 (12.4)	134 (13.1)
Treatment for hypertension	92 (8.7)	99 (9.7)
Current smoker	73 (6.9)	73 (7.1)
Treatment with statin	55 (5.2)	72 (7.0)
History of diabetes	25 (2.4)	19 (1.9)

Source: ISS, Appendix 1.3.2.1

Table 55 Open-label Study: Baseline Cardiovascular Risk Factors

	Zavegepant 10 mg N=1023 n(%)
Cardiovascular risk factors contraindicating triptans	
Ischemic coronary artery disease	0
Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders arrhythmias	1 (0.2)
History of stroke or transient ischemic attack	3 (0.5)

Peripheral vascular disease	0
Ischemic bowel disease	0
Uncontrolled hypertension	0
General risk factors	
Family history of coronary artery disease	65 (10.8)
Treatment for hypertension	40 (6.6)
Current smoker	28 (4.6)
Treatment with statin	29 (4.8)
History of diabetes	3 (0.5)

Source: Study 202 CSR, Table 14.1.5.3

In the controlled studies, the applicant did not note any cardiovascular AEs in patients taking 10 mg zavegepant. Below is a table of AEs that I assess to be potentially cardiovascular, cerebrovascular, and peripheral vascular AEs of zavegepant for the controlled (Table 56) studies and open-label study (Table 57). There was an SAE of thrombosis in a zavegepant-treated patient (see section 8.4.2) In the open-label trial there was a cerebrovascular accident that occurred (see section 8.4.2).

Table 56 Controlled Studies: Summary for Preferred Terms for Potential Cardiovascular, Cerebrovascular, and Peripheral Vascular Disease AEs

Preferred Term	Placebo N=1056 n(%)	Zavegepant 10 mg N=1023 n(%)
Atrioventricular block	1 (0.1)	0
Cardiac murmur	1 (0.1)	0
ECG QT prolonged	0	2 (0.2)
Hypertension	1 (0.1)	0
Supraventricular extrasystoles	1 (0.1)	0
Syncope	1 (0.1)	0
Thrombosis	0	1 (0.1)

Source: SCS, ADAE dataset for study 201 and 301

Reviewer comment: No clinically meaningful imbalances were identified between the placebo and zavegepant groups.

Table 57 Open-label Study: Summary for Preferred Terms for Potential Cardiovascular, Cerebrovascular, and Peripheral Vascular Disease AEs

Preferred Term	Zavegepant 10 mg N=603

	n(%)
Ataxia	1 (0.2)
Atrial fibrillation	1 (0.2)
Carotid bruit	1 (0.2)
Cerebrovascular accident	1 (0.2)
ECG abnormal	1 (0.2)
ECG QT prolonged	1 (0.2)
ECG T wave abnormal	1 (0.2)
Heart rate increase	1 (0.2)
Hypertension/blood pressure increase	3 (0.5)
Palpitations	3 (0.5)
Syncope	2 (0.3)

Source: Study 202, ADAE dataset

Additionally, there was a death in study 302 with cause of death on autopsy states as hypertensive cardiovascular disease. Please see section 8.4.1 of this review for further details.

Hypertension

In the controlled studies there was a total of one hypertension TEAE, in a placebo-treated patient. In the open-label study, there was one patient who withdrew from the study during the safety follow-up period due to hypertension. There were 3 (0.5%) patients total who experienced TEAEs of hypertension. Two were mild and one was moderate in severity.

8.5.2. Hepatotoxicity

Given the concern for potential hepatotoxicity with small molecule GCRP receptor inhibitors, the Division had recommend conducting a two- to three-month study with 300 migraine patients or healthy volunteers, using zavegepant on a near daily basis with a comparator arm. The applicant did not use a comparator arm in study 106 and in response to an IR on March 5, 2021, stated that if there were significant events in the 3 times the upper limit of normal (ULN) for AST/ALT or two times the ULN for bilirubin categories, then they would perform another safety study with a placebo arm for comparison. Study 106 was conducted to address the hepatotoxicity evaluation with 100 mg oral zavegepant (see section 3.2). A consultation was requested for the Drug-induced Liver Injury (DILI) team who reviewed the studies 201, 301, 202, and 106.

Design of open-label, 8-week safety, hepatotoxicity study (study 106)

Study 106 was a multi-center, Phase 1, open-label, study that included daily dosing for 8 weeks in healthy subjects. Subjects were to administer 100 mg oral zavegepant every day for 8 weeks. Subjects returned to the study site for the week 2, week 4, week 6, week 8/EOT visits, follow-up

week 2, and follow-up week 4 visits. At the week 4 visit, subjects were required to dose in person at the study site to assess PK.

In study 106, there were 13 (3.6%) patients with AEs that led to discontinuation. Five subjects had LFT abnormality AEs after taking at least one dose of zavegepant and three subjects had CK increase leading to discontinuation.

Table 58 Study 106: Adverse Events Leading to Discontinuations

MedDRA System Organ Class Serious Adverse Event (Preferred Term)	Zavegepant 100 mg N=364 n(%)
Any AE	13 (3.6)
Investigations	8 (2.2)
Blood creatine phosphokinase increased	3 (0.8)
Liver function test increased	2 (0.5)
Alanine aminotransferase increased	1 (0.3)
Aspartate aminotransferase increased	1 (0.3)
Blood bilirubin increased	1 (0.3)
Glomerular filtration rate decreased	1 (0.3)
Liver function test abnormal	1 (0.3)
Gastrointestinal disorders	2 (0.5)
Abdominal pain upper	1 (0.3)
Diarrhea	1 (0.3)
Nausea	1 (0.3)
Infections and infestations	2 (0.5)
Coronavirus infection	1 (0.3)
COVID-19	1 (0.3)
Psychiatric disorders	2 (0.5)
Anxiety	1 (0.3)
Nightmare	1 (0.3)
General disorders and administration site conditions	1 (0.3)
Pyrexia	1 (0.3)
Nervous system disorders	1 (0.3)
Presyncope	1 (0.3)
Respiratory, thoracic and mediastinal disorders	1 (0.3)
Nasal congestion	1 (0.3)

Source: Study 106 CSR, table 14.3.2.3A

The most common (≥2%) TEAEs in study 106 were headache, nausea, and blood creatine phosphokinase increase.

Table 59 Study 106: TEAEs **≥1%**

Preferred Term	Zavegepant 100 mg N=364 n (%)
Headache	25(6.9)
Nausea	12(3.3)
Blood creatine phosphokinase increased	10(2.7)
Constipation	5(1.4)
Dyspepsia	5(1.4)
Diarrhea	4(1.1)
Dizziness	4(1.1)
Liver function test increased	4(1.1)
Myalgia	4(1.1)
Weight increased	4(1.1)

Source: OCS Analysis Studio, Safety Explorer. Filters: TRT01A = "ZAVEGEPANT" and SAFFL = "Y" (ZAVEGEPANT); TRTEMFL = "Y" (Adverse Events). Percent Threshold: ZAVEGEPANT ≥ 1%.

Table 60 Study 106: SOC of Investigations TEAEs

Preferred Term	Zavegepant 100 mg N=364 n (%)
Investigations	26(7.1)
Blood creatine phosphokinase increased	10(2.7)
Liver function test increased	4(1.1)
Weight increased	4(1.1)
Aspartate aminotransferase increased	2(0.5)
Blood pressure increased	2(0.5)
Alanine aminotransferase increased	1(0.3)
Blood bilirubin increased	1(0.3)
Glomerular filtration rate decreased	1(0.3)
Hemoglobin decreased	1(0.3)
Heart rate increased	1(0.3)
Liver function test abnormal	1(0.3)
Sars-cov-2 test positive	1(0.3)

Source: OCS Analysis Studio, Safety Explorer. Filters: TRT01A = "ZAVEGEPANT" and SAFFL = "Y"

(ZAVEGEPANT); TRTEMFL = "Y" (Adverse Events).

Overall the DILI team did not find a significant DILI risk with the intranasal zavegepant. The review noted that the majority (84%) of the cases of concern were considered as liver injury not due to DILI. There were no Hy's Law cases and no clear imbalances in liver enzyme elevations in the controlled studies. There were noted modest transaminase elevations in the repeat dose in studies 202 and 106. However, The DILI team felt that at the dosing used in the studies the risk of DILI is low. The DILI team recommended standard pharmacovigilance and no substantial labeling for hepatotoxicity. Please refer to Dr. Ling Lan's consultation review for further details.

Reviewer comment: Although the DILI team did not find a significant DILI risk with IN zavegepant, there does appear to be modest transaminase elevations in the repeat dose studies 202 and 106. There is a potential that patients could use zavegepant more often than what is allowed on the label. In addition, there is still a concern for potential hepatotoxicity in this drug class. Given this we would recommend that there be enhance pharmacovigilance for hepatotoxicity.

8.5.3. Gastrointestinal Effects

There is a theoretical concerns that CGRP antagonists could inhibit the protective effects that CGRP provides for the gastric system. Specifically, there are theoretical concerns for gastric ulcer, bowel ischemia, and constipation.

In the controlled study, there were 53 (5.2%) patients treated with 10 mg zavegepant who experienced at least one GI disorder SOC categorized AE and 14 (1.3%) patients in the placebo-treated patients with GI-related AEs. Of the individual AEs, nausea and vomiting each demonstrated a higher percentage incidence in zavegepant-treated patients compared to placebo-treated patients, while the rest of the GI-related AEs did not demonstrate a clinically significant imbalance. Nausea occurred in 36 (3.5%) zavegepant-treated patients and in 9 (0.9%) placebo-treated patients. While vomiting occurred in 16 (1.6%) zavegepant-treated patients and in 3 (0.3%) placebo-treated patients. There were no AEs of constipation.

In the open label study, there were two GI-related SAEs: bile duct stenosis, and appendicitis. Each SAE occurred in a different patient, and neither patient discontinued zavegepant due to these SAEs. There were four patients who had who withdrew due to the AEs of nausea, vomiting, or both nausea and vomiting. Another patient withdrew due to esophagitis. In the open-label study there were 89 (14.8%) patients who had at least one AE categorized in the system organ class (SOC) of GI disorders. Three (0.5%) had constipation in the open-label study. None of these constipation AEs led to withdrawal.

Reviewer comment: There is a notable imbalance especially in the overall GI-related TEAEs. However, much of the imbalance is due to the TEAEs of nausea and vomiting. Constipation has been reported in other CGRP antagonists. There were no AEs of constipation in the controlled

studies. In the open-label study there were three AEs of constipation, although none led to withdrawal.

8.5.4. Suicidality Assessment

The controlled studies (201 and 301) and the open-label study (202) utilized the Sheehan Suicidality Tracking Scale (S-STS) to assess patients for suicidality. In the open-label study, S-STS was measured bi-weekly for the first month then monthly.

In the controlled studies there was no clinically meaningful imbalance in the mean or median change from baseline in S-STS score comparing zavegepant 10 mg to placebo. In study 201, the 10 mg group had no changes from the baseline score of zero. There were 4 patients who had a change of 1 in the other zavegepant-treated (5 mg and 20 mg) and placebo-treated groups, with one each in the 5 mg and 20 mg groups, and 2 in the placebo group. There was one patient with >1 change in the S-STS score from the 5 mg group. For the controlled studies (201 and 301), there were no TEAEs of suicidality reported in the zavegepant arm. There were two in the placebo arm.

In the open-label study (202), there were no TEAEs of suicidality in patients during the on-treatment period or during follow-up. There was one patient who was discontinued due to a positive S-STS score >0, who had a score of 18 on study day 168. No AE of depression or suicidality was reported. The patient did have a past medical history of psychiatric disorders which included depression, anxiety, and insomnia. There were two other patients who had worsening of S-STS score of 1 from baseline at any time after treatment initiation.

Reviewer comment: There does not appear to be a suicidality signal.

8.5.5. Local Toxicity

The applicant included in their review of local irritation AEs select preferred terms (PTs) based on installation site reactions, upper respiratory tract signs and symptoms, and dysgeusia. In my review, I added to the applicant's PTs the following: taste disorder, ageusia, olfactory nerve disorder, nasal edema, nasal inflammation, nasal congestion, acute sinusitis, epistaxis, nasal dryness, nasal mucosal disorder, nasal ulcer, sinus congestion, sinusitis, nasal mucosal disorder, nasopharyngitis, rhinitis allergic, sinonasal obstruction, sinus pain, anosmia, and rhinitis.

In the controlled studies, there were 354 reported local irritative TEAEs. In the zavegepant group there were 269 TEAEs with 263 (97.8%) of those TEAEs categorized as mild or moderate. In the placebo group, 84 out of 85 (98.8%) TEAEs were rated as mild or moderate in intensity. There were six zavegepant-treated patients with 6 TEAEs that had not resolved. Two of the TEAEs are ongoing and the other four were lost to follow-up. Two patients experienced the two TEAEs that were ongoing, and both were mild nasal congestion. Overall, there were 222 (21.7%) zavegepant-treated patients and 79 (7.5%) of placebo-treated patients who experienced at

least one local irritative AE.

Table 61 Controlled Study (201 and 301): Local Irritative TEAEs

Preferred Term	Placebo N=1056 n(%)	Zavegepant 10 mg N=1023 n(%)
Taste disorder*	46 (4.4)	184 (18.0)
Nasal discomfort	8 (0.8)	27 (2.6)
Nasal congestion**	10 (0.9)	12 (1.2)
Throat irritation	1 (0.1)	12 (1.2)
Epistaxis	2 (0.2)	5 (0.5)
Oropharyngeal pain	2 (0.2)	5 (0.5)
Rhinorrhea	2 (0.2)	4 (0.4)
Sneezing	2 (0.2)	4 (0.4)
Rhinalgia	0	3 (0.3)
Upper airway cough syndrome	2 (0.2)	3 (0.3)
Sinus discomfort***	2 (0.2)	2 (0.2)
Sinus headache	1 (0.1)	2 (0.2)
Sinusitis****	2 (0.2)	2 (0.2)
Nasal dryness	1 (0.1)	1 (0.1)
Nasopharyngitis	2 (0.2)	1 (0.1)
Oropharyngeal discomfort	0	1 (0.1)
Nasal mucosal disorder	1 (0.1)	0
Nasal ulcer	1 (0.1)	0

Source: Reviewer created using ISS ADAE, AELOCIFL=Y, and other specific AEs
*Taste disorder includes dysgeusia, ageusia, and taste disorder
**Nasal congestion includes rhinitis, nasal edema, nasal inflammation, nasal congestion
***Sinus discomfort includes sinus congestion, paranasal sinus discomfort, sinus pain
****Sinusitis includes sinusitis, and acute sinusitis

Reviewer comment: There are 3 TEAEs that demonstrate a notable imbalance between the zavegepant and placebo groups. Those are taste disorder, nasal discomfort, and throat irritation. Taste disorder and nasal discomfort are recommended to be included in the PI since it occurs in more than 2% of the zavegepant arm and is at least 1% greater than the placebo arm.

There was a total of 904 reported local irritative TEAEs. Of those 890 (98.5%) were mild or moderate in intensity. Most local irritative TEAEs resolved with only 20 patients experiencing 24 (2.6%) TEAEs that were either ongoing (13), unknown (10), or recovered with sequelae (1). The 13 TEAEs that were ongoing occurred in 11 patients. Eight of those TEAEs appear to be reports bad taste or dysgeusia after each use of the spray. Those TEAEs included rhinitis/nasal

inflammation (2), rhinorrhea (1), nasal discomfort (1), and sneezing (1). The patient with nasal discomfort withdrew. The patient who recovered with sequelae, reported mild nasal burning intermittently after using zavegepant and still completed the study.

Table 62 Open-label Study (202): Local Irritative TEAEs

Preferred Term	Zavegepant 10 mg N=603 n(%)
Taste disorder*	250 (41.5)
Nasal discomfort	62 (10.3)
Nasal congestion**	41 (6.8)
Throat irritation	33 (5.5)
Rhinorrhea	21 (3.5)
Sneezing	15 (2.5)
Epistaxis	14 (2.3)
Oropharyngeal pain	14 (2.3)
Sinusitis***	12 (2.0)
Nasopharyngitis	11 (1.8)
Sinus discomfort****	9 (1.5)
Rhinalgia	8 (1.3)
Nasal mucosal disorder	5 (0.8)
Upper-airway cough syndrome	5 (0.8)
Oropharyngeal discomfort	4 (0.7)
Nasal dryness	3 (0.5)
Anosmia	2 (0.3)
Olfactory nerve disorder	1 (0.2)
Sinonasal obstruction	1 (0.2)
Upper respiratory tract congestion	1 (0.2)

Source: Reviewer created using study 202 ADAE, AELOCIFL=Y, and other specific AEs
*Taste disorder includes dysgeusia, ageusia, and taste disorder
**Nasal congestion includes rhinitis, nasal edema, nasal inflammation, rhinitis allergic, nasal congestion
***Sinusitis includes sinusitis, and acute sinusitis
****Sinus discomfort includes sinus congestion, paranasal sinus discomfort, sinus pain

8.6. Safety Analyses by Demographic Subgroups

Below are the rates of TEAEs by sex, age, and race for the open-label, long-term, safety study (study 202). Of the 603 patient, 459 (76.1%) experienced at least one TEAE.

Table 63 Open-Label, Long-Term, Safety Study (202): Rates of TEAEs by Sex, Age, and Race in Patients Exposed to Zavegepant

	Sex		Age		Race		
	F N=517 n(%)	M N=86 n(%)	<40 years N=264 n(%)	≥40 years N=339 n(%)	White N=502 n(%)	Black N=70 n(%)	Other N=31 n(%)
Patients experiencing TEAEs	402 (77.8)	57 (66.3)	200 (75.8)	259 (76.4)	389 (77.5)	51 (72.9)	19 (61.3)

Source: OCS Analysis Studio, Custom Table Tool. Columns - Dataset: Demographics; Filter: SAFFL = 'Y'. Table Section 1 - Dataset: Adverse Events; Filter: TRTEMFL = 'Y'.

Reviewer comment: The rate of TEAEs in the subgroups were similar to the percentage of TEAEs of the entire population except for males and in the subgroup of patients whose race was neither black nor white. Both of these subgroups were small, which makes drawing a definitive conclusion difficult.

8.7. Specific Safety Studies/Clinical Trials

8.7.1. Study BHV3500-110

Study 110 was a Phase 1, single-center, randomized, partially-blind, placebo-controlled, 1-arm drug-drug-interaction (DDI) study in healthy subjects to evaluate the effects of zavegepant and concomitant sumatriptan on resting blood pressure. Subjects were administered sumatriptan succinate injection as two 6 mg SC injections separated by one hour, for a total dose of 12 mg on days 1 and 4. Zavegepant 20 mg IN (divided into two 10 mg sprays) or placebo was administered daily for 3 consecutive days from day 2 to day 4. On day 4, zavegepant or placebo was administered immediately after the second sumatriptan SC injection. Blood samples for sumatriptan and zavegepant PK were collected on day 1 and day 3, respectively, and again on day 4 for both drugs. Blood pressure recordings were taken 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 blood pressure readings were analyzed as a time-weighted average over the recording interval. The primary objective was to evaluate the effect of zavegepant on resting BP when administered concomitantly with sumatriptan in healthy subjects.

A total of 42 subjects received at least one dose of any study drug, which were included in the safety evaluation. There were no deaths, SAEs, or TEAEs that led to discontinuation. Thirty-eight of 42 (90.5%) subjects experienced at least 1 TEAEs during the study. Of those patients, 25 (59.5%) patients received sumatriptan, 31 (88.6%) subjects received zavegepant, 28 (80.0%)

subjects received sumatriptan + zavegepant, 5 (83.3%) subjects received placebo alone, and 4 (66.7%) subjects receiving placebo + sumatriptan).

The most common reported TEAEs were dysgeusia (34 [81.0%]); head discomfort and throat irritation (11 [26.2%] subjects each); headache, paresthesia, nausea (9 [21.4%] subjects each); dizziness and pharyngeal paresthesia (7 [16.7%] subjects each); and nasal discomfort and discomfort (6 [14.3%] subjects each).

There were no significant changes in the time-weighted average (TWA) of mean arterial pressure, DBP, and SBP after administration of sumatriptan (SC 12 mg) + zavegepant (IN 20 mg) or sumatriptan + placebo compared to sumatriptan alone. The difference in TWA of DBP and SBP between the treatments of sumatriptan + zavegepant and sumatriptan was 0.00 mmHg, and 0.33 mmHg, respectively (Table 64 and Table 65).

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Table 64 Study 110: Summary of Blood Pressure Parameters by Treatment

Treatment	Day	N	TWA*		
			MAP	DBP	SBP
Sumatriptan	1	41	86.902 (5.979)	72.097 (6.239)	116.214 (8.570)
Zavegepant	3	35	83.871 (6.722)	69.040 (6.841)	114.094 (9.120)
Placebo	3	6	81.000 (6.925)	66.705 (5.555)	109.157 (9.313)
Sumatriptan + zavegepant	4	35	87.163 (6.754)	72.346 (6.803)	116.829 (10.170)
Sumatriptan + placebo	4	6	85.053 (6.666)	70.000 (6.690)	112.825 (8.275)

BP = blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; N = number of subjects dosed; SBP = systolic blood pressure; SD = standard deviation; TWA = time-weighted average
*The TWA for all BP measurements is presented as mean (SD).

Table 65 Study 110: Statistical Comparison of Blood Pressure Parameters Between the Treatments of Sumatriptan + Zavegepant and Sumatriptan

Parameter	LSM (mmHg)		Comparison (Sumatriptan + Zavegepant vs. Sumatriptan)			
	Sumatriptan + zavegepant	Sumatriptan	Difference (mmHg)	90% CI	P-value (Treatment)	P-value (Group)
TWA of MAP	86.79	86.75	0.04	-0.69,	0.924	0.0154
TWA of DBP	71.97	71.97	0.00	-0.76,	0.995	0.0210
TWA of SBP	116.39	116.06	0.33	-0.97,	0.669	0.1042

Source: Study 110 CSR, Table 11-2

Reviewer comments: There does not appear to have been a significant change in BP parameter when administering sumatriptan SC 12 mg and zavegepant 20 mg IN compared to sumatriptan alone. Also of note is that the 20 mg zavegepant dose is double the proposed 10 mg dose in this application.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

To review the open-label, safety study for human carcinogenicity or tumor development, I searched TEAEs by the SOC of "neoplasm benign, malignant and unspecified (incl cysts and polyps)". There were three patients with a reported malignancy: one with a basal cell carcinoma of the left shin, one patient with a malignant melanoma, and one patient with squamous cell carcinoma of both the neck and left leg. There was one patient with an acoustic neuroma.

Reviewer comment: There does not appear to be a signal at this time for the development of malignancies, however the number of malignancies is small. Therefore, I am unable to draw a definitive conclusion about the carcinogenicity of zavegepant.

8.8.2. Human Reproduction and Pregnancy

Although there was a requirement for contraception and exclusion of pregnant and lactating women, some patients became pregnant and were inadvertently exposed to zavegepant. As of the 120-safety update there were 19 reported pregnancies. Of the 19 reported pregnancies 13 patients received at least 1 dose of zavegepant, 3 were screen failures, 1 subject was placebo, 1 pregnancy was in a partner of a subject who received zavegepant, and 1 other patient was randomized but did not receive study drug. In Table 66, the outcomes of the pregnant subjects potentially exposed to zavegepant are listed.

Table 66 Summary of Pregnancy and Outcomes in Patients Exposed to Zavegepant

Birth Outcome	
Full term birth without complications	5*+
Voluntary termination	4
Spontaneous abortion	1
Negative pregnancy test after positive	3
Ongoing	1
Total	14

Source: Reviewer created with data from ISS, Appendix 7E
*Includes pregnancy of a partner of a study subject who received zavegepant

[+]Includes a patient with suspected sudden infant death syndrome 2.5 weeks after full term birth

Based on the defining a pregnancy exposure period starting on the date of conception (last menstrual period plus 14 days) minus 5 half-lives, there were 7 exposures and 1 possible exposures in patients who received zavegepant. Using this definition the pregnancy outcomes are listed in Table 67.

Table 67 Summary of Pregnancy Outcomes in Patients Exposed during Pregnancy Exposure Period

Birth Outcome	
Full term birth without complications	4[+]
Voluntary termination	3
Negative pregnancy test after positive	1*
Total	8

Source: Reviewer created with data from ISS, Appendix 7E
[+]Includes a patient with suspected sudden infant death syndrome 2.5 weeks after full term birth
*Includes a patient with a possible exposure during pregnancy exposure period

8.8.3. Pediatrics and Assessment of Effects on Growth

Patients under the age of 18 years were excluded from all studies and were not exposed to zavegepant. Therefore, this subsection is not applicable to this review.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The applicant defined PTs used to identify potential drug abuse related AEs. This list included the MedDRA SMQ for "drug abuse, dependency, and withdrawal" and other PTs identified by the applicant. In total the list included >750 PTs.

In the zavegepant development program there was one reported overdose in a patient (study 202) who administered two dose of zavegepant 10 mg IN in 24 hours. No other AEs were reported in this patient.

The Controlled Substance Staff (CSS) was consulted when the NDA was received. Prior to the NDA submission CSS had previously attended and provided consultation for the End-of of Phase 2 meeting on March 16, 2020. After the applicant provided 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, as requested, Dr. James M. Tolliver (CSS consultation review dated July 23, 2020) reviewed the documents. CSS concluded there was no abuse potential signal associated with zavegepant

based on the completed preclinical and clinical studies, therefore the applicant did not need to conduct preclinical drug discrimination, intravenous self-administration, or physical dependence studies or human abuse potential studies. The applicant was instructed to still monitor for adverse events indicative of abuse potential, as well as for actual incidences of abuse, misuse, or diversion.

CSS concluded that the abuse-related safety data in the NDA did not demonstrate an abuse potential signal for zavegepant and was consistent with the known profile of approved CGRP antagonists (rimegepant and ubrogepant), which are not scheduled under the Controlled Substances Act (CSA). CSS recommended 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." Please see Dr. Steven Galati's review.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Since zavegepant is not currently marketed in any country, this section is not applicable to this application.

8.9.2. Expectations on Safety in the Postmarket Setting

The applicant attempted to evaluate zavegepant in a population representative of the migraine population in the U.S. The demographics of the population are similar to the U.S. population, although the percentage of >65 was not similar. Due to the inclusion and exclusion criteria for the studies excluding patients with conditions such as recent myocardial infarction, stroke, BMI ≥35 kg/m^2, and major psychiatric disorders, the population is likely healthier than the general population of the U.S. These exclusions may restrict the generalizability of the safety data to the likely broader U.S. migraine population.

8.9.3. Additional Safety Issues From Other Disciplines

None

8.10. Integrated Assessment of Safety

The safety review for this NDA focused on the two double-blind, placebo-controlled studies and the open-label, long-term, safety study. Theoretical safety issues that were of interest were cardiovascular, cerebrovascular, peripheral vascular, gastrointestinal, and local toxicity. In addition, hepatotoxicity was also of concern given the previous development of other early small molecule CGRP receptor antagonists. The applicant performed an open-label study with oral zavegepant to evaluate this concern. Overall, my review did not identify any serious safety

issues that would preclude marketing of zavegepant. The safety issues identified could be handled with labeling and enhanced pharmacovigilance.

The review of AEs related to the cardiovascular, cerebrovascular, and peripheral vascular systems did not identify overall safety concerns in regard to zavegepant usage. An issue that may limit the overall assessment of cardiovascular, cerebrovascular, and peripheral vascular risk with zavegepant usage, is the generally healthier study population than the general U.S. population. In addition, the study population contained a smaller number of patients greater than 65 years of age compared to the general U.S. population. Lastly, due to the reported case of a hypertensive cardiovascular disease leading to death, I recommend enhanced pharmacovigilance for myocardial infarction.

Regarding GI toxicity, nausea was the second most prevalent AEs in the controlled studies. Nausea and vomiting were the main GI-related TEAEs responsible for the imbalance between zavegepant and placebo. There were no AEs of constipation in controlled studies. There were three in the open-label study there were three, but none led to withdrawal.

Hepatotoxicity was also of concern. There were no cases of Hy's law found in the review of the controlled studies, open-label, long-term, safety study, and of the hepatotoxicity study.

Overall, there is still theoretical concerns regarding cardiovascular and cerebrovascular risk since the study population had fewer patients over the age of 65 and had essentially excluded major cardiovascular disease. Given this and the context of the reported death due to hypertensive cardiovascular disease and SAE of cerebrovascular accident, I recommend that enhanced pharmacovigilance for myocardial infarction, and stroke. Pharmacovigilance of MI and stroke are currently conducted in the postmarketing setting for other drug product in zavegepant's drug class. In addition, given that there did appear to be modest transaminase elevations in the repeat dose studies and the concern of hepatotoxicity in this drug class, I recommend enhanced pharmacovigilance for hepatoxicity in the postmarketing setting.

9. Advisory Committee Meeting and Other External Consultations

N/A

10. Labeling Recommendations

10.1. Prescription Drug Labeling

At the time of this review, the final label was not completed. I have the following recommendations for the PI:

In section 6, I recommend combining taste disorder, ageusia, and dysgeusia combined under the term "taste disorder" for the controlled study adverse reactions. This combination would change the percentages in the proposed label from 17% for "dysgeusia" to 18% for "taste disorder" under the zavegepant column. I would also recommend that vomiting be included in the table of adverse reactions.

In section 14, I recommend an efficacy table for study 2 as below:

Table 68 Efficacy Endpoints in Study 201

	Placebo	ZAVZPRET 10 mg
Pain Freedom at 2 hours postdose		
n/N	62/401	88/391
% Responders	15.5	22.5
Difference from placebo (%)		7.0
p-value		0.011
MBS freedom at 2 hours postdose		
n/N	135/401	164/391
% Responders	33.7	41.9
Difference from placebo (%)		8.3
p-value		0.016

In section 14 of the PI, for study 201, I do not recommend including any secondary endpoints since none were statistically significant. For study 301, I recommend describing the following secondary endpoints:

1. Pain relief at 2 hours
2. Return to normal function at 2 hours
3. Sustained pain freedom from 2 to 48 hours
4. Freedom from photophobia at 2 hours
5. Freedom from phonophobia at 2 hours

10.2. Nonprescription Drug Labeling

N/A

11. Risk Evaluation and Mitigation Strategies (REMS)

N/A

12. Postmarketing Requirements and Commitments

PMRs

1. Deferred pediatric studies required under the Pediatric Research Equity Act. There is an agreed upon Initial Pediatric Safety Plan (iPSP) for a full waiver for patient less than 6 years old and a deferral for ages 6 through 17 years. The applicant is required to complete the following:

    - A juvenile animal toxicology study in one species.
    - A pharmacokinetic, safety, and tolerability study in pediatric migraine patients 6 to less than 12 years of age.
    - A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of zavegepant for the acute treatment of migraine (with or without aura) in pediatric patients 6 to less than 18 years of age. This study must be designed to show superiority of zavegepant over placebo.
    - A long-term open-label safety study of zavegepant in migraine patients 6 to less than 18 years of age, for up to one year. This study should include a minimum of 200 patients treating on average, one migraine attack per month for 6 months; and 75 patients treating, on average, at least one migraine attack per month for one year.

2. Pregnancy registry and outcomes study

Enhanced Pharmacovigilance

1. Myocardial infarction
2. Stroke
3. Hepatotoxicity

Reviewer comment: Previous drug products in the same class (small molecule CGRP receptor antagonists) have had the enhanced pharmacovigilance for myocardial infarction and stroke. In zavegepant's development program there has been a cerebrovascular accident in the open-label, long-term safety study using zavegepant 10 mg IN, and a death related to suspected

hypertensive cardiovascular disease. Although the patient who cerebrovascular accident is unlikely related to zavegepant, I do believe continued pharmacovigilance for myocardial infarction and stroke is still prudent in the drug class given the theoretical concerns related to the mechanism of action.

Given that there were modest transaminase elevations in the repeat dose studies and that there is a concern for potential hepatotoxicity in this drug class, we recommend enhanced pharmacovigilance for hepatotoxicity.

13. Appendices

13.1. References

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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 201, 202, 301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1474		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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03/08/2023 04:59:45 PM

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03/09/2023 07:11:44 AM