CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216386Orig1s000

SUMMARY REVIEW

Summary Review

Date	March 9, 2023
From	Heather Fitter, MD Paul R. Lee, MD, PhD Teresa Buracchio, MD
Subject	Summary Review
NDA #	216386
Applicant	Pfizer Inc.
Date of Submission	March 9, 2022
PDUFA Goal Date	March 9, 2023
Proprietary Name	Zavzpret
Established or Proper Names	Zavegepant
Dosage Form(s)	Nasal Spray
Applicant Proposed Indication(s)/Population(s)	Acute treatment of migraine with or without aura in adults
Applicant Proposed Dosing Regimen(s)	Single dose of 10 mg nasal spray; Maximum dose in 24 hour period of 10 mg
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Acute treatment of migraine with or without aura in adults
Recommended Dosing Regimen(s)	Single dose of 10 mg nasal spray; Maximum dose in 24 hour period of 10 mg

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Zavegepant is a new molecular entity (NME) developed for the acute treatment of migraine with or without aura in adults. This is the first intranasally administered calcitonin gene-related peptide (CGRP) receptor antagonist to be reviewed in an FDA marketing application.

There are many FDA-approved drugs for the acute treatment of migraine with or without aura in adults, including triptans (5-$HT_{1B/1D}$ receptor agonists), lasmiditan (5-HT_{1F} receptor agonist), dihydroergotamine (DHE), certain non-steroidal anti-inflammatory drugs ([NSAIDs] which can be used alone or in combination with a triptan), and ubrogepant and rimegepant (oral CGRP receptor antagonists). In addition, there are over-the-counter products marketed for migraine. The use of some of the marketed prescription medications described above (i.e., triptans, ergotamines, and NSAIDs) for the acute treatment of migraine is restricted in patients with cardiovascular (CV) disease. Although lasmiditan is not restricted in patients with CV disease, there is a restriction regarding driving, specifically that patients should avoid driving for 8 hours after dosing. There are currently four injectable monoclonal antibodies that target the CGRP system and two oral agents that are indicated for the preventive treatment of migraine in patients with chronic migraine and/or episodic migraine. These products do not appear to be associated with increased CV risk.

The efficacy of zavegepant was demonstrated in two adequate and well-controlled studies. The studies used well-validated and clinically meaningful endpoints to establish efficacy; the proportion of subjects who were pain-free and most bothersome symptom (MBS)-free at 2 hours after dosing for the acute treatment of a migraine attack. One study evaluated the efficacy and safety of 5 mg, 10 mg, and 20 mg doses of zavegepant administered intranasally compared to placebo, and the other study evaluated the efficacy and safety of a 10 mg dose of zavegepant administered intranasally compared to placebo. The 10 mg zavegepant dose was effective and demonstrated statistically significant superior results on both co-primary endpoints compared to placebo in both studies. In the study that included multiple dose arms, the 20 mg zavegepant dose also demonstrated statistically significant superior results on both co-primary endpoints but with a flat dose response as compared to the 10 mg dose. The 5 mg dose did not demonstrate statistically significant superiority to placebo on the co-primary endpoints. The treatment effect size for pain freedom at 2 hours post-dose was approximately 7-9% greater than placebo for the 10 mg dose (zavegepant responder rate of approximately 23-24%). The treatment effect size for MBS-freedom at 2 hours was approximately 8-9% greater than placebo for the 10 mg dose (zavegepant responder rate of approximately 40-42%).

The safety profile of zavegepant was characterized in these two controlled efficacy studies, and a long-term open-label study with repeat dosing. Additionally, a dedicated hepatic safety study was conducted because of the occurrence of serious hepatotoxicity with previous oral CGRP receptor antagonists that are no longer in development. No serious toxicities were identified in these trials. Common adverse events in clinical trials that occurred in at least 1% of zavegepant-treated subjects included taste disorders, nausea, nasal discomfort, vomiting, throat irritation, nasal congestion, and fatigue/somnolence. The clinical trials supporting this application included generally younger, healthy subjects and effectively excluded subjects with major CV disease. The data provided with this application do not support the need for CV restrictions with the use of zavegepant; however, these data are too limited to definitively establish the CV safety of zavegepant.

The risk/benefit profile of zavegepant is acceptable and supports approval for the acute treatment of migraine with or without aura in adults. There is no evidence to suggest that zavegepant is more effective than other FDA-approved drugs for the acute treatment of migraine; however, zavegepant is the first intranasal CGRP receptor antagonist to be approved and may offer a needed treatment alternative to some patients. Labeling will clearly convey the generally favorable safety profile demonstrated in this application which includes an increase in the incidence of alterations in taste, nausea, nasal discomfort, and vomiting as compared with placebo.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Migraine is a primary headache disorder characterized by recurrent headaches that are moderate to severe, accompanied by various associated symptoms. The typical headache of migraine is throbbing, unilateral, and aggravated by motion, but bilateral and/or non-throbbing headaches are also commonly reported. Typical migraine-associated symptoms include nausea, vomiting, photophobia, and phonophobia, but a myriad of other neurological symptoms may occur, and various degrees of cognitive impairment are often present. Migraine attacks typically last from 4 to 72 hours in adults. About one-third of people with migraine experience transient neurological symptoms before and/or during an attack, referred to as a migraine aura. • Migraine was found to be the second highest cause of disability in the Global Burden of Disease Study in 2016. The prevalence of migraine is approximately 9% in males and 20% in females in the U.S., thus resulting in a major impact to public health.	Migraine is a serious and frequently disabling condition that can impact the quality of patients' lives.

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td>Current Treatment Options</td><td>• There are many FDA-approved therapies for acute migraine such as triptans, dihydroergotamines (DHE), lasmiditan, oral CGRP receptor antagonists, and certain non-steroidal anti-inflammatory drugs (NSAIDs), the latter which can be used alone or in combination with a triptan. Triptans and DHE are contraindicated in patients with cardiovascular (CV) disease and NSAIDS have labeling that warns patients of the risk of CV events with the use of these products. Lasmiditan includes a restriction on driving for 8 hours following a dose and does not allow for a second dose within 24 hours. In addition, there are several over-the-counter drugs marketed for migraine.</td><td>Several classes of drugs are indicated for the acute treatment of migraine with or without aura in adults. However, many patients still do not respond adequately to these therapies.

A nasally administered medication in the CGRP antagonist class for the acute treatment of migraine could be an important treatment option for some patients.</td></tr>
<tr><td>Benefit</td><td>• The efficacy of zavegepant was demonstrated in two adequate and well-controlled clinical studies (Studies 201 and 301). The studies used well-validated and clinically meaningful endpoints to establish efficacy, the proportion of subjects that are pain-free (PF) at 2 hours post-dose, and most bothersome symptom (MBS)-free at 2 hours post-dose. Results are summarized in the table below; comparisons between the zavegepant 10 mg groups and placebo are highly statistically significant.
<table>
<tr><th></th><th>PF at 2 hours (%)</th><th>Placebo corrected PF (%)</th><th>MBS free at 2 hours (%)</th><th>Placebo corrected MBS free (%)</th></tr>
<tr><td>Study 201</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Placebo</td><td>15.9</td><td></td><td>33.7</td><td></td></tr>
<tr><td>Zavegepant 10 mg</td><td>22.5</td><td>7.0</td><td>41.9</td><td>8.3</td></tr>
<tr><td>Study 301</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Placebo</td><td>14.9</td><td></td><td>31.1</td><td></td></tr>
<tr><td>Zavegepant 10 mg</td><td>23.6</td><td>8.8</td><td>39.6</td><td>8.7</td></tr>
</table>
• These studies did not evaluate the efficacy of a second dose for a single migraine attack. Therefore, efficacy or safety of a second dose has not been established and the maximum dose that will be labeled is a single dose of 10 mg IN in a 24 hour period.</td><td>Zavegepant is effective for the acute treatment of migraine with or without aura in adults.

The recommended doses of zavegepant for marketing will be 10 mg intranasally (IN) administered. The maximum dose that should be administered in a 24-hour period is 10 mg. Therefore, a second dose for a single migraine attack, should not be taken.</td></tr>
</table>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The most common treatment emergent adverse events (TEAEs) in the pooled Phase 3 controlled clinical trials of zavegepant-treated subjects included taste disorders (18% zavegepant vs 4% placebo), nausea, (4% zavegepant vs 1% placebo), nasal discomfort (3% zavegepant vs 1% placebo), and vomiting (2% zavegepant vs <1% placebo). • The rate of adverse dropouts was low and there was no clear pattern of adverse event (AE) that led to withdrawal during the controlled trials. • Clinical trials included generally younger, healthy subjects and effectively excluded subjects with major CV disease. • Based on either the proposed mechanism of action or previous safety issues seen with CGRPs, safety issues of concern for zavegepant were CV, cerebrovascular, gastrointestinal, and hepatotoxicity. No clear safety signals were detected upon review of these issues. • A thorough QT study showed no significant QT prolongation at supratherapeutic doses and no clinically meaningful effect on mean PR or QRS intervals. • No serious safety issues related to the use of zavegepant were identified during this review. Other uncertainties • The risk of adverse outcomes in pregnancy has not been characterized. • Safety and efficacy in pediatric migraine patients has not been established.	There were no significant safety findings that would preclude approval of zavegepant. Adequate labeling and enhanced pharmacovigilance will address the identified safety issues. The data submitted with this application do not support the need to include CV restrictions in labeling. However, these data are also insufficient to definitively establish the CV safety of zavegepant. Because the risk of adverse outcomes in pregnancy has not been characterized, and because zavegepant will be used in women of childbearing potential, a pregnancy registry, and a pregnancy outcomes study will be postmarketing requirements (PMR). Since safety and efficacy of zavegepant in pediatric migraine patients have not been established, postmarketing studies to evaluate zavegepant in pediatric migraine patients will be required under the Pediatric Research Equity Act (PREA). There should be enhanced pharmacovigilance with periodic evaluation of CV events, cerebrovascular events, and hepatotoxicity.

2. Background

This review discusses the data presented by Pfizer Inc. (the applicant) in support of a new drug application (NDA) for zavegepant nasal spray for the acute treatment of migraine with or without aura in adults. Zavegepant is a calcitonin gene-related peptide (CGRP) receptor antagonist intended for nasal administration.

Migraine is a primary headache disorder characterized by recurrent headaches that are moderate to severe, accompanied by various associated symptoms. The typical headache of migraine is throbbing, unilateral, and aggravated by motion, but bilateral and/or non-throbbing headache is also commonly reported. Typical migraine-associated symptoms include nausea, vomiting, photophobia, and phonophobia, but a range of other neurological symptoms may occur, with various degrees of cognitive impairment often present. Migraine attacks typically last between 4 to 72 hours in adults. About one-third of individuals with migraine experience transient neurological symptoms before and/or during a migraine attack, referred to as migraine aura. Generally accepted diagnostic criteria for migraine are presented in the International Classification of Headache Disorders (ICHD).

Many products are FDA-approved for the acute treatment of migraine in adults. These products include a number of different triptans, dihydroergotamine, nonsteroidal anti-inflammatory drugs (NSAIDs) used alone or in combination with a triptan, and a 5-HT_{1F} agonist, lasmiditan, and orally administered CGRP receptor antagonists, such as rimegepant and ubrogepant. In addition, there are many over-the-counter medications that are labeled for the acute treatment of migraine. However, not all migraineurs respond well to the available therapies, the use of which can also be limited by safety concerns (e.g., restrictions for the use of triptans, ergotamines, and NSAIDs in patients with cardiovascular [CV] disease.) Four monoclonal antibodies targeting the CGRP system have been approved for the preventive treatment of both chronic and episodic migraine: erenumab (Aimovig) targeting the CGRP receptor, and fremanezumab (Ajovy), galcanezumab (Emgality), and eptinezumab (Vyepti), targeting the CGRP peptide.

As noted above, there are several products approved for the migraine population in the CGRP antagonist class, and, to date, no serious safety signals have been identified outside of hypersensitivity. Previously, development of other small molecules in this class has been limited by serious hepatotoxicity. Therefore, the Division had requested that all sponsors developing products in this class conduct focused hepatotoxicity assessments to evaluate their products' potential for hepatotoxicity. Therefore, this applicant conducted a dedicated daily dosing study over 8 weeks for this purpose.

The applicant provides data from two placebo-controlled efficacy trials, Studies BHV3500-201 (referred to as Study 201 in this review) and Study BHV3500-301 (referred to as Study 301 in this review) in subjects with migraine with or without aura to support the efficacy of zavegepant for the proposed indication. Study 201 evaluated three dose levels (5 mg, 10 mg, or 20 mg) and Study 301 evaluated a single dose of 10 mg. Both studies were single attack studies in adult subjects with migraine with or without aura. The applicant only proposes the

10 mg dose for marketing. The applicant provides one year data from an open-label repeat dosing long-term safety study (Study BHV3500-202) to support the safety of chronic intermittent use and also provides data from an open-label, repeat daily dosing study (Study BHV3500-106) over eight weeks to evaluate the potential for hepatotoxicity.

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Martha Heimann (refer to her review for the entire OPQ list of participants in the review of this application).

Drug Substance

The free base of zavegepant demonstrated instability and was, therefore, not suitable for commercial development. The hydrochloride salt was selected for development instead. This form is a white to off-white powder that is highly soluble in water. The drug product formulation is an aqueous solution for intranasal administration.

Dr. Heimann states that the submission contains an adequate description of the manufacturing process, and that the four proposed regulatory starting materials are adequate. Starting material specifications, including controls on impurities, are adequately justified. The drug substance release specification provide sufficient controls on the identity, purity, and strength of the drug substance. The seven related substance impurities listed in the specification are adequately controlled. Supporting and registration batch data are provided and are within specifications. The proposed retest period for the drug substance is (b) (4) months. The proposed retest period is supported by the provided long-term and accelerated stability data and OPQ recommends that this (b) (4)-month retest period be granted.

Drug Product

Zavegepant is a novel CGRP receptor antagonist developed for the treatment of migraine. Zavegepant nasal spray, 10 mg is a ready to use unit dose, disposable nasal spray drug-device combination product. The drug product is formulated as a (b) (4) mg/mL solution and filled into a glass vial, stoppered with a rubber plunger, and assembled into (b) (4) nasal spray device. The device delivers a single spray of (b) (4) uL containing 10 mg of zavegepant. The proposed specification is acceptable. The tests and acceptance criteria are adequate to ensure the product quality through the proposed shelf life of the product. The performance attributes of the spray device meet the standards of the FDA Guidance for nasal products. The data provided demonstrates that the applicant can manufacture the drug product with consistent quality. The primary components of the container closure system meet the United States Pharmacopeia (USP) requirements. The applicant has provided up to 12 months of long-term, up to 12 months of intermediate-term, and up to 6 months of accelerated stability data for three primary batches of the drug product. OPQ states that the drug product may be granted a shelf-life of 24 months, when stored under controlled room temperature.

Microbiology

The specifications comply with USP microbial limit recommendations, method suitability testing for nonsterile products intended for nasal use and met the regulatory expectations for the product release specification.

The overall manufacturing inspection recommendation is approval for all facilities associated with this application.

The OPQ review teams has determined that the applicant has provided adequate information on the proposed drug product to ensure the identity, strength, quality, and purity of the proposed drug product. OPQ recommends approval of this application from a quality perspective.

4. Nonclinical Pharmacology/Toxicology

The primary nonclinical reviewer for this application was Dr. Elizabeth Khoury, with Dr. Lois Freed performing the secondary review. A standard battery of nonclinical studies was conducted. Refer to Dr. Khoury's review of this NDA for a detailed discussion of these studies. The following are among the key conclusions from these studies:

- There were no effects of zavegepant on cardiovascular or respiratory safety pharmacology endpoints, and human ether-a-go-go related gene (hERG) half maximal inhibitory concentration (IC50) was in excess of 30 μM.
- Intranasal toxicology studies up to 6- and 9-months' duration were conducted in Sprague Dawley (SD) rat and cynomolgus monkey, respectively. Primary toxicity in rat consisted of olfactory and respiratory epithelium degeneration/regeneration which resolved during the recovery period. A no-observed-adverse-effect level (NOAEL) of 12.5 mg/day was established. The primary toxicities in monkeys consisted of decreased weight gain and olfactory and respiratory epithelium degeneration/regeneration. A NOAEL of 45 mg/day (15 mg/kg) was established.
- Zavegepant was not mutagenic or clastogenic in a standard genotoxicity battery. A 26-week transgenic mouse study and a 2-year rat study were conducted to assess carcinogenicity. Both were negative for carcinogenicity.
- Reproductive and developmental toxicology studies were conducted in rats and rabbits. There were no reproductive or developmental toxicities at doses resulting in drug exposures at least 2,000-fold higher than human exposure at the proposed clinical dose. A juvenile animal toxicology study was submitted in November 2022 and will be listed as a PMR.

Drs. Khoury and Freed conclude that the nonclinical data are adequate to support approval of this NDA.

5. Clinical Pharmacology

The primary reviewers for the Office of Clinical Pharmacology (OCP) were Dr. Suresh Naraharisetti and Dr. Jie Liu; Dr. Gopichand Gottipati and Dr. Atul Bhattaram were the Team Leaders. The OCP review states that the clinical pharmacology information included in this NDA support approval of the 10 mg dose administered as a single spray ((b) (4) μL) in one nostril using the (b) (4) unit-dose system. The maximum dose in a 24-hour period is 10 mg.

Mechanism of Action
Dr. Naraharisetti states that zavegepant is a CGRP receptor antagonist, and that CGRP receptors are reported to be upregulated in migraine. CGRP levels in the cranial circulation are thought to be increased during a migraine attack, and CGRP itself has been shown to trigger migraine-like headache. He notes that there were seven other drugs in this class approved in recent years for either the preventive treatment of migraine, the acute treatment of migraine, or for the combined indication.

Absorption
Zavegepant has a Tmax of approximately 0.5 hours after intranasal (IN) administration of 10 mg. Following once daily dosing of zavegepant IN spray for 14 days, there is minimal accumulation. Zavegepant exhibits slightly less than dose-proportional increase in exposure following a single IN dose administration over the dose range of 1 mg to 40 mg. The OCP review states that zavegepant 10 mg IN is not expected to have a food effect, and therefore it is acceptable that the applicant did not evaluate the impact of food-intake on pharmacokinetics (PK).

Distribution
Plasma protein binding of zavegepant is approximately 90%. The mean apparent volume of distribution of zavegepant is 1774 L.

Metabolism and Elimination
Zavegepant is primarily metabolized by cytochrome P450 (CYP)3A4, based on in-vitro data. The results from a mass-balance study showed that the hepatic metabolism of zavegepant was low and did not show major circulating metabolites. Fecal excretion is the main route of elimination of unchanged zavegepant (80%) and renal clearance was a minor pathway (11%) in excretion of zavegepant based on the mass balance study. Zavegepant has an effective elimination half-life of 6.5 hours.

Drug-Drug Interactions
Based on in-vitro studies, zavegepant is not an inhibitor nor an inducer of CYP enzymes. In a dedicated drug-drug interaction (DDI) study, the concomitant administration of IN zavegepant with itraconazole (a strong CYP3A4 and P-gp inhibitor), did not result in a clinically relevant effect on zavegepant exposure.

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

Zavegepant is a substrate for OATP1B3 and NTCP transporters. In a dedicated DDI study, the concomitant administration of single oral dose of 100 mg zavegepant with steady state rifampin (strong inducer of CYP3A and P-gp, inhibitor of OATP1B3 and NTCP) resulted in a 2.3-fold and 2.2-fold increase in zavegepant AUC and Cmax respectively. This magnitude of interaction is a composite of the induction effect on P-gp and CYP3A (resulting in decreased

zavegepant exposures) as well as the inhibition effect on OATP1B3 and NTCP transporters (resulting in increased zavegepant exposures). Therefore, the magnitude of the observed OATP1B3 and NTCP transporter-mediated interactions noted above are likely underestimates. The applicant proposed (b) (4) The OCP team disagrees with this proposal and recommends avoiding the use of zavegepant with inhibitors of OATP1B3 or NTCP transporters. The applicant conducted PBPK modeling and simulation under certain scenarios (e.g., single dose of rifampin, which they proposed inhibits only OATP1B3 and NTCP, and cyclosporine, an inhibitor of OATP1B3 and NTCP). The OCP team reviewed this information and negotiated labeling and the possibility of requesting a PMR using this information. Following negotiations with the applicant, agreement was reached on labeling to avoid use of zavegepant with inhibitors of OATP1B3 and NTCP transporters, and that a postmarketing study was not required.

The applicant did not conduct a dedicated study to evaluate the impact of OATP1B3 or NTCP inducers on PK of zavegepant. Concomitant administration of zavegepant with inducers of OATP1B3 or NTCP transporters may result in reduced plasma concentrations of zavegepant. Therefore, the OCP team recommends avoiding the concomitant use of zavegepant with inducers of OATP1B3 or NTCP transporters since this may result in a decrease in zavegepant exposure.

Special Populations/Intrinsic Factors

Clinical studies demonstrated that subjects with moderate hepatic impairment have a 1.9-fold increase in zavegepant AUC and 16% increase in Cmax as compared to healthy matched control. No dose adjustment needs to be made for mild or moderate hepatic impairment, but patients with severe hepatic impairment should avoid use. The applicant recommended (b) (4) (b) (4) However, the OCP review team recommends that no dose adjustment needs to be made for moderate hepatic impairment because the effective half-life of zavegepant is 6.5 hours, and so even with once daily use, minimal accumulation should occur. The labeling will state that the safety of treating more than 8 migraines in a 30-day period has not been established; so it is unlikely that there will be any accumulation with multiple dosing with appropriate routine use of zavegepant. Other factors supporting this recommendation are the fact that zavegepant does not undergo hepatic metabolism, and that no major metabolites were identified in the mass balance study. It is contextually important to note that the safety profile for zavegepant was reasonably characterized in two adequate and well-controlled trials without a concerning adverse event profile, and this suggestion of safe use is supported further by cumulative safety data generated from several recently approved drugs in the same class.

The renal route plays a minor role in the clearance of zavegepant (11% of unchanged drug excreted in urine). In subjects with creatinine clearance in the range from 52 to greater than 90 mL/min there appears to be no clinically significant effect on PK of zavegepant. The impact of severe renal impairment and kidney failure on zavegepant PK was not studied.

In patients with severe renal impairment, accumulation of uremic solutes may inhibit OATP transporter, resulting in increased exposures of zavegepant. Further, the impact of dialysis on PK of zavegepant was not studied. Therefore, the OCP review team recommends avoiding use

of zavegepant in patients with severe renal impairment (CLcr 15 – 29 ml/min) or kidney failure (CLcr < 15 ml/min).

Other DDI studies:

With Ethinyl estradiol-levonorgestrel and Sumatriptan:

Two dedicated DDI studies were conducted to evaluate the effect of IN zavegepant 20 mg dose on single dose PK of combined oral contraceptives, ethinyl estradiol-levonorgestrel (CYP3A4 substrates), and single dose PK and pharmacodynamics (blood pressure elevation) of sumatriptan. Both studies did not show clinically relevant effects.

Nasal Decongestants

The OCP team concluded that nasal decongestants may affect the absorption of concomitantly administered nasal products, and that the evidence in literature did not provide clarity regarding whether nasal decongestants could interfere with IN zavegepant. Taking a conservative approach, the OCP team recommends avoiding concomitant administration of nasal decongestants with zavegepant. If concomitant use cannot be avoided, nasal decongestants should be administered at least 1 hour after zavegepant administration. This 1-hour interval is consistent with Tmax of IN zavegepant (0.5 to 1 hour) and would ensure that the majority of absorption of zavegepant has occurred before a nasal decongestant is introduced.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical - Efficacy

Dr. Ryan Kau conducted the clinical efficacy review for this application. Dr. Ye Li conducted the primary biometrics review, and Dr. John Lawrence was the biometrics Team Leader.

The applicant conducted two placebo-controlled efficacy trials (Table 1) in adult migraine subjects with or without aura: Study 201 and Study 301.

Table 1: Clinical Efficacy Studies

	Population	Treatment Duration	Doses	Location
Study 201	Migraine with or without aura	Single attack	5 mg, 10 mg, or 20 mg	U.S.
Study 301	Migraine with or without aura	Single attack	10 mg	U.S.

Study 201

Study 201 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of an intranasal dose of zavegepant for the acute treatment of a single migraine attack. Subjects were randomized in a 1:1:1:1 ratio to either 5 mg zavegepant, 10 mg zavegepant, 20 mg zavegepant, or placebo. There was no option for taking a second dose to treat the initial migraine. Subjects had 45 days after randomization to treat a migraine headache of moderate or severe intensity with investigational product (IP).

Patients eligible for enrollment into Study 201 were adults 18 years of age and older with at least a one-year history of migraine with or without aura. Subjects had to be diagnosed with migraine before the age of 50 years and have a history of no more than 8 migraine attacks of moderate to severe intensity per month within the last 3 months before screening. Patients with uncontrolled hypertension or clinically significant cardiovascular or cerebrovascular disease were excluded. Patients with a myocardial infarction, cardiac surgery, transient ischemic attack, or stroke within 6 months prior to screening were excluded.

The co-primary endpoints used to establish efficacy were the proportion of subjects with headache pain freedom at 2 hours, and the proportion of subjects with most bothersome symptom (MBS) freedom at 2 hours post dose. Pain freedom was defined as the absence of migraine pain at 2 hours following the treatment of a qualifying migraine attack (migraine of moderate to severe intensity). The MBS for a qualifying migraine attack was defined as either nausea, phonophobia, or photophobia, and was to be determined at study migraine attack onset before taking study drug. The statistical analysis plan specified that both co-primary endpoints would have to be statistically significant in favor of zavegepant in order to consider the study supportive of a treatment effect. The applicant included multiple (15) secondary endpoints and included a statistical plan to control for multiple comparisons. This review will focus on the following clinically meaningful endpoints that were considered for inclusion in labeling: pain-relief at 2 hours, return to normal function at 2 hours, sustained pain freedom from 2 to 48 hours, photophobia freedom at 2 hours, and phonophobia freedom at 2 hours.

The co-primary endpoints were analyzed using Cochran-Mantel-Haenszel tests stratified by preventive migraine medication use at randomization. Subjects that used rescue medication at or before 2 hours post-dose and subjects with missing response status at 2 hours post-dose were classified as failures for both co-primary endpoints. The applicant controlled the overall Type 1 error rate for multiple comparisons using the following strategy: if the co-primary endpoint tests were both significant for zavegepant versus placebo, the secondary endpoints were tested for zavegepant versus placebo using a hierarchical gate keeping procedure, with each test in the hierarchy conducted at a 2-sided alpha level 0.0167 in Study 201 and at a 2-sided alpha level 0.05 in Study 301, respectively.

The mITT population was defined by the applicant as all subjects who received IP, recorded a migraine of moderate to severe intensity, and had at least 1 post-dose efficacy measurement. All efficacy analyses were conducted on the mITT population.

Study 301

Study 301 was a multicenter, randomized, double-blind, placebo-controlled, parallel-arm study to evaluate the safety and efficacy of IN zavegepant vs placebo for the treatment of migraine with or without aura. Subjects were randomized in a 1:1 ratio to either zavegepant 10 mg, or placebo. Other details regarding the study design above for Study 201 were identical to those of this study except where differences were noted above, and therefore will not be repeated within this review. Of note, Study 201 was designed as a dose finding, Phase 2/3 study that compared 3 doses of zavegepant to placebo, while Study 301 was considered a Phase 3 efficacy study that compared a single dose (selected based on the results of Study 201) to placebo.

Results

Studies 201 and 301

The median age of the subjects in both trials was between 39 and 40 years. Most subjects (81-87%) were female, and most (76-84%) were White. Demographic characteristics were generally balanced between treatment groups in each study with no clinically significant differences.

Baseline disease characteristics were balanced between treatment groups in both trials.
The median of the average number of migraine/month by history was 5, and approximately 23-29% of subjects experienced migraine with aura, and 13-14% of subjects were on concomitant preventive migraine treatment.

Co-primary endpoints

Table 2 presents the results of the primary efficacy analyses for Studies 201 and 301.

Table 2: Study 201 and 301- Co-primary Endpoint Efficacy Results

		Study 201			Study 301	
	Placebo	Zavegepant			Placebo	Zavegepant
		5 mg	10 mg	20 mg		10mg
N	**401**	**387**	**391**	**402**	**646**	**623**
PF at 2 hours, n (%)	62 (15.5)	76 (19.6)	88 (22.5)	93 (23.1)	96 (14.9)	147 (23.6)
p-value		0.1214*	0.0113	0.0055		<0.001
MBS Free at 2 hours n (%)	135 (33.7)	151 (39)	164 (41.9)	171 (42.5)	201 (31.1)	247 (39.6)
p-value		0.1162*	0.0155	0.0094		0.0012

*p-value is not statistically significant
Source: modified from Dr. Li's biometrics review Tables 8, 9, 15, and 16

Drs. Kau and Li both conclude that treatment with zavegepant resulted in statistically significant increases in the proportion of subjects reporting pain freedom at 2 hours post-dose

and MBS freedom at 2 hours post-dose as compared to placebo for the 10 mg and 20 mg dose in Study 201 and for the 10 mg dose in Study 301.

Secondary endpoints

Study 201

The secondary endpoints were tested hierarchically at a 2-sided 0.0167 significance level and the first secondary endpoint, pain relief at 2 hours post-dose, was not significant for any zavegepant dose group. All secondary endpoints listed after the secondary endpoint of pain relief at 2 hours post-dose were formally reported because of the hierarchical testing strategy and the failure of the first tested endpoint to achieve statistical significance. Of interest, the secondary endpoints that will be described in labeling based on the results of Study 301, that also demonstrated nominal significance in Study 201 were pain relief at 2 hours, sustained pain freedom from 2 to 48 hours, return to normal function at 2 hours, and photophobia freedom at 2 hours.

Study 301

Statistically significant improvements were demonstrated on the secondary endpoints pain relief at 2 hours, return to normal function at 2 hours, sustained pain freedom from 2 to 48 hours, phonophobia freedom at 2 hours, and photophobia freedom at 2 hours (see Table 3).

Table 3: Study 301- Results for Secondary Endpoints

	Study 301	
	Placebo	**10 mg**
Pain Relief at 2 Hours, n (%)	**321 (49.7)**	**366 (58.7)**
N	**646**	**623**
Difference from placebo (%)		9.0
p-value		0.0012
Return to Normal Function at 2 Hours, n (%)	**152 (25.6)**	**204 (35.8)**
N	**593**	**570**
Difference from placebo (%)		10.2
p-value		0.0001
Sustained Pain Freedom 2-48 Hours, n (%)	**56 (8.7)**	**77 (12.4)**
N	**646**	**623**
Difference from placebo (%)		3.7
p-value		0.0308
Phonophobia Freedom at 2 Hours, n (%)	**139 (32.7)**	**167 (41.0)**
N	**425**	**407**
Difference from placebo (%)		8.3
p-value		0.0123
Photophobia Freedom at 2 Hours, n (%)	**167 (28.5)**	**207 (37.1)**
N	**585**	**558**
Difference from placebo (%)		8.6
p-value		0.0018

Source: modified from Dr. Li's biometrics review Tables 17, 18, 19, 20 and 21

Efficacy by Subgroups

Dr. Li performed analyses of the treatment effect across subgroups for both Studies 201 and 301, and concluded that the efficacy trends observed in the co-primary analyses appeared to be similar across the subgroups age, gender, and African American race. The subgroup, "Asian and Race other than Asian", did not demonstrate a statistically significant treatment effect; however, no definitive conclusions can be made based on the small sample sizes represented within these subgroup comparisons.

Efficacy Conclusions

The applicant has provided substantial evidence of effectiveness of zavegepant based on the results from two adequate and well-controlled trials. Both studies were conducted in subjects with migraine with or without aura, and both demonstrated significant increases in the proportion of subjects who were pain-free at 2 hours post-dose and MBS-free at 2 hours post-dose in the zavegepant 10 mg group, as compared to placebo. The analyses of the trials' secondary endpoints were supportive of the primary efficacy analyses only in Study 301. In Study 201, efficacy on the co-primary endpoints for the 10 mg and 20 mg doses demonstrated a flat dose response; therefore, only the 10 mg dose was included in Study 301. The inability of Study 201 to demonstrate positive results on the secondary endpoints may have been due to the smaller sample sizes assigned to the individual treatment groups. Study 201 was designed to evaluate the efficacy of multiple doses as compared to placebo, and therefore each treatment arm had less power to identify a treatment effect on the secondary endpoints. Nevertheless, the findings from Studies 201 and 301 demonstrated that the 10 mg dose is effective, and this will be the only dose recommended for marketing. The efficacy of a second dose within 24 hours was not evaluated; therefore, the recommended dose should be a single dose of 10 mg within a 24-hour period.

8. Safety

Dr. Ryan Kau conducted the clinical safety review of this application.

As discussed by Dr. Kau, the overall exposure to zavegepant exceeds the minimum number of subjects recommended by the International Council for Harmonization (ICH) E1 Guideline for chronically administered medications. He reports that 3120 subjects were exposed to at least one dose of zavegepant, of which 1038 were exposed in the controlled clinical trials and 1660 received at least one dose of zavegepant 10 mg. Three hundred and sixty subjects treated at least 2 migraines per month for at least 6 months' duration, and 298 subjects treated at least 2 migraines per month for 12 months' duration.

Dr. Kau notes that the migraine studies excluded patients with uncontrolled, unstable, or recent cardiovascular disease, hepatic or biliary disorders, and patients 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. He suggests that these exclusions may limit the generalizability of the safety data to the larger population when considering that postmarketing use will be much less restrictive.

There were no obvious demographic imbalances between active treatment and placebo when considering, gender, age, race, ethnicity, or weight.

Deaths

No deaths were reported in the primary studies reviewed to support this application, specifically Studies 201, 301, 202 (the 52 week open label long term safety study), and 106 (the 8 week daily dosing oral hepatotoxicity study).

There was one death in Study 302, an ongoing Phase 2/3 dose blind, randomized, placebo-controlled safety and efficacy dose-ranging study (100 mg or 200 mg oral formulation) of zavegepant for the preventive treatment of migraine. A 60 year-old male with a history of diverticulitis, lower back pain, and amoxicillin hypersensitivity received zavegepant on the same day he was mountain biking and was reportedly "pronounced dead at the scene from a heart attack". The autopsy report stated that he died due to hypertensive cardiovascular disease. Dr. Kau reports that the subject collapsed while mountain biking. Concomitant medications included fish oil and glucosamine. The subject also took sumatriptan as needed and took his last dose of sumatriptan 3-4 days before this event. The subject was noted to have elevated blood pressure at screening and a grade 1 systolic murmur. The ECG at screening was read as "normal". The applicant had a cardiac electrophysiologist review this ECG tracing and noted that it was "noisy" but revealed sinus bradycardia of 58 beats per minute (bpm). The week 4 ECG also demonstrated sinus bradycardia at 52 bpm, with atrial and ventricular premature complexes. The subject developed bronchitis 15 days prior to his death which was reported as mild in intensity and treated with dextromethorphan for 3 days. Toxicology results detected caffeine with no other positive findings. COVID-19 testing was negative.

The diagnoses listed on the autopsy report were hypertensive cardiovascular disease with cardiac hypertrophy, left ventricular hypertrophy, arteriolonephrosclerosis, aortic atherosclerosis and pulmonary edema. Dr. Kau considers that a relationship of this event to study drug is possible given the temporal relationship between study drug administration and the death, yet he notes that there were confounding factors since the subject appears to have had underlying diagnoses of mild hypertension, cardiac hypertrophy, and atherosclerosis which are chronic conditions, that were likely present at the time of trial enrollment and prior to the use of zavegepant. I agree with this assessment and consider the case to be confounded by the presence of underlying cardiac disease, and therefore a clear relationship of this event to study drug administration cannot be determined.

Serious Adverse Events (SAEs)

Dr. Kau notes that there were few overall SAEs. There were two SAEs reported in a single subject following zavegepant administration in the controlled clinical trials. A 24-year-old female subject developed a lower extremity deep vein thrombosis (DVT) following a motor vehicle accident that was discovered during her hospitalization which occurred 12 days following her last dose of zavegepant. The motor vehicle accident was caused by another driver that was speeding and struck the subject from behind, and therefore does not appear related to any preceding adverse event on the part of the subject. The subject was on concomitant weekly ethinylestradiol/norelgestromin transdermal patch which was initiated 2 months prior to the DVT. Dr. Kau considers this SAE unlikely to be related to drug administration due to the lack of a reasonable temporal relationship of these two events (12 days after last dose would represent over 44 half-lives for zavegepant) and the concomitant use of birth control pills, a known risk factor for venous thrombosis.

In the open-label study, there were 9 subjects that experienced 11 SAEs after receiving at least one zavegepant dose. The reported SAEs were cerebrovascular accident (described in greater detail below), fall, concussion, pseudo syncope, back pain, pneumonia, pleurisy, appendicitis,

herpes zoster meningoencephalitis, multiple sclerosis, and bile duct stenosis. No SAE occurred more than once. These SAEs are unlikely to be related to study drug administration.

Given the theoretical concern for CGRP inhibition to reduce compensatory mechanisms in the setting of ischemia, the case of cerebrovascular accident is described below.

A 28-year-old female with a history of seasonal allergy, dysmenorrhea on no concomitant medications developed right sided weakness, visual changes, and headache 8 days after her last dose of zavegepant. On arrival to the emergency room she had a National Institute of Health Stroke Scale (NIHSS) score of 7 and a computed tomography (CT) angiography (CTA) of the head that showed a left posterior cerebral artery (PCA) P2 branch occlusion. She was also noted to have speech difficulty, right hemianopsia, reduced facial sensation in the distribution of the trigeminal nerve (V)2 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. A CT perfusion scan showed a left occipital lobe (20 mL) ischemic penumbra without cortical infarct. A rapid diffusion study was performed which confirmed an area of reversible ischemia without evidence of infarct. Head CT without contrast was negative. The subject was given intravenous alteplase. Magnetic resonance imaging (MRI) of the brain 1 day after admission revealed an acute left thalamic infarction. MR angiography was consistent with recanalization of the PCA. A hypercoagulability panel showed a mixed picture for antiphospholipid syndrome. Lupus anticoagulant was positive, ANA positive at 1:80, dilute Russell Viper Venom Test was weakly positive. The subject had no history of other symptoms related to antiphospholipid antibody syndrome such as venous thrombosis, early pregnancy loss, or known heart disease. Symptoms resolved over two days and the subject's diagnosis was a CVA due to thrombosis of the PCA. Stroke workup demonstrated a small defect within the interatrial septum consistent with a patent foramen ovale (PFO). The subject had a PFO closure procedure 29 days after onset of this SAE. The subject reports taking 3 doses of zavegepant prior to onset of the SAE within 30 days before the event. Following this event, the subject discontinued zavegepant. Of interest, 11 days prior to this event the subject reported chest discomfort, headache and oropharyngeal pain which were considered resolved 3 days later. The subject missed a visit 7 days after onset of these AEs due to "COVID-19 symptoms" although a rapid COVID-19 test was negative.

This SAE was identified as a potential adverse event of special interest given the general concern for CGRP antagonism leading to worse outcomes with ischemic events. Following review of this case, Dr. Kau considers it unlikely for this SAE to be related to study drug administration given that the last dose of study medication was taken 8 days before this event (over 30 half-lives following drug administration), and there were alternate plausible etiologies identified including a PFO and possible hypercoagulable state .

Discontinuations

In the controlled trials, there were no adverse events leading to treatment discontinuations. In the open label trials there were 45 subjects that experienced adverse events leading to discontinuation. Those that occurred more commonly are 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%]). Many of these adverse events (i.e., dysgeusia, nasal discomfort, throat irritation, rhinorrhea) are expected and unavoidable because of the intranasal presentation. Liver transaminase elevations are discussed in a subsequent sub-section.

Treatment Emergent Adverse Events (TEAEs)

Table 4, modified from Dr. Kau's review, displays the most common TEAEs from the controlled trials occurring greater than or equal to 1% and greater than placebo which are taste disorders (which includes dysgeusia and ageusia), nausea, nasal discomfort, vomiting, throat irritation, nasal congestion, and fatigue/somnolence.

Table 4: Studies 201 and 301: Pooled TEAEs occurring in the Double-Blind Treatment Period with an incidence of at Least 1% and Greater than Placebo

Preferred Term	**Placebo (N=1056) n (%)**	**Zavegepant 10 mg (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)	2
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

*Taste disorders include taste disorder, dysgeusia, and ageusia
**Nasal congestion includes nasal congestion, rhinitis, nasal edema, and nasal inflammation
Source: modified from Dr Kau's clinical review Table 39

The TEAE profile of zavegepant from the long-term safety trial is similar to that described in the controlled trials.

Local Toxicity Findings

Dr. Kau reports that in the controlled trials 22% of subjects in the zavegepant 10 mg group and 8% of subjects in the placebo group experienced local irritation AEs. Those that occurred at an incidence of over 2% and greater than placebo were taste disorders (which includes dysgeusia and ageusia) and nasal discomfort (see Table 4 above). These particular AEs (taste disorders and nasal discomfort) are not unexpected for an intranasal product. Most of these adverse events were rated as mild or moderate in intensity. There were six zavegepant-treated subjects that had 5 local irritative TEAEs that were not reported as resolved. Two are ongoing and are adverse events of nasal congestion, rated as mild. Four of the ongoing TEAEs have an unknown outcome because these subjects were lost to follow up. The local irritation AEs that were described in the open-label long-term extension trial that occurred at an incidence of over 2% were taste disorders (42%), nasal discomfort (10%), nasal congestion (7%), throat irritation (6%), rhinorrhea (4%), sneezing (3%), epistaxis (2%), and sinusitis (2%).

Laboratory Findings

Dr. Kau did not find clinically meaningful differences in the controlled trials between zavegepant, and placebo mean changes from baseline compared to placebo for all laboratory measures except for the mean change from baseline for creatine kinase (CK). The magnitude of this change was small (12 U/L point difference) and did not appear clinically significant. The outlier analysis of CK after treatment did not demonstrate an imbalance between zavegepant and placebo, and there was no signal for myopathy in the current safety database.

Sumatriptan and Zavegepant Interaction Study

The applicant conducted a Phase 1 drug-drug interaction study (Study BHV3500-110) to evaluate the effects of zavegepant and concomitant sumatriptan on resting blood pressure. Dr. Kau states that there was not a significant change in blood pressure parameters when sumatriptan 12 mg was administered subcutaneously (SC) with zavegepant 10 mg administered IN, as compared to sumatriptan alone. This study also included dosing of zavegepant at 2 times the dose planned for marketing so there is a suggestion that even if zavegepant were used outside of its appropriate dosing with sumatriptan that there would not be a significant risk of an interaction causing clinically significant elevated blood pressure.

Vital Signs

Dr. Kau notes that treatment with zavegepant did not appear to result in clinically significant changes in vital signs with respect to analyses of mean values of heart rate, temperature, and blood pressure, as well as outliers in both the controlled efficacy trials and in the Phase 1 studies at the dose planned for marketing.

Electrocardiogram (ECG)

Dr. Kau found no clinically significant changes from baseline in mean heart rate (HR), PR interval, QRS, or QTcF, as compared to placebo in the controlled phases of the zavegepant clinical trials.

Dr. Kau notes that in the controlled studies, there were two ECG-related TEAEs of ECG QT prolonged in the 10 mg zavegepant group and none in the placebo group. The subjects who experienced these ECG events were not symptomatic. In the open-label long-term safety study, there were two subjects with different ECG-related TEAE. One subjected experienced a mild TEAE of ECG QT prolonged and the other subject was reported to have moderate TEAEs of ECG T wave abnormal and ECG abnormal.

The applicant conducted individual and pooled concentration-QTc analyses of single ascending dose (SAD) and multiple ascending dose (MAD) studies (BHV3500-101 and BHV3500-102) which was reviewed by the Interdisciplinary Team for QT Studies (QT-IRT). The QT-IRT 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. 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. The QT-IRT recommends including the following statement in labeling: “At a dose 4 times the maximum approved recommended daily dose, <Tradename> does not prolong the QT interval to any clinically relevant extent.”

Cardiovascular Risk

Dr. Kau did not identify any potential CV or cerebrovascular safety concerns regarding toxicity associated with the use of zavegepant, noting that his review is limited in this respect, because the population studied was primarily young and healthy. The applicant included some subjects over the age of 65 in the studies; however, the overall representation of CV, cerebrovascular, and peripheral vascular disease in the clinical trial population was low.

Dr. Kau notes that there was no imbalance in cardiovascular AEs in the controlled studies for zavegepant but notes two SAEs related to vascular disease. As discussed, the subject with thrombosis was using an oral contraceptive medication which has a known association with thrombosis, and therefore this event appears unrelated to zavegepant use. The subject who died due to a cardiovascular event while mountain biking had underlying cardiac disease and therefore this case is confounded but given the temporal relationship of the event to the last dose of zavegepant a relationship to study drug cannot be ruled out.

Dr. Kau concludes that the current database does not support an association of increased CV risk with zavegepant, and that labeling should not include CV restrictions. However, these data are also insufficient to definitively establish the CV safety of zavegepant, and enhanced pharmacovigilance in the post-market setting will be required.

Gastrointestinal Toxicity

Gastrointestinal effects, such as constipation, diarrhea, and nausea, as well as intermittent cases of bowel ischemia were seen with other products in this class, therefore gastrointestinal (GI) events are adverse events of special interest. In the controlled studies, there were 53 (5.2%) subjects treated with 10 mg zavegepant who experienced at least one GI-related AE and 14 (1.3%) subjects in the placebo-treated group with GI-related AEs. Of the individual AEs, nausea and vomiting each demonstrated a higher incidence in zavegepant-treated subjects compared to placebo-treated subjects, while the rest of the GI-related AEs did not demonstrate a clinically significant imbalance. Nausea occurred in 36 (3.5%) zavegepant-treated subjects and in 9 (0.9%) placebo-treated subjects. While vomiting occurred in 16 (1.6%) zavegepant-treated subjects and in 3 (0.3%) placebo-treated subjects. There were no AEs of constipation.

In the open-label study, there were two GI-related SAEs: bile duct stenosis, and appendicitis. Neither subject discontinued zavegepant due to these SAEs. There were four subjects who withdrew due to the AEs of nausea, vomiting, or both nausea and vomiting. Another subject withdrew due to esophagitis. In the open-label study, there were 89 (14.8%) subjects 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.

Hepatotoxicity Risk

Hepatotoxicity was a safety signal of interest for this class of medication as described above. Dr. Paul Hayashi from the Drug Induced Liver Injury (DILI) team conducted a review of the data provided regarding this potential signal in this application.

The applicant provides data from several databases to address this concern, namely, the safety

database from the controlled clinical trials (Studies 201 and 301), the open-label safety study (Study 202), and a study in 364 healthy volunteers who received zavegepant 100 mg oral tablets daily for 8 weeks (Study 106). Dr Hayashi reports that he assessed 32 cases of potential DILI across the four studies. Of the 32, he deemed 27 as unlikely DILI or indeterminate. Alternate diagnoses were myopathy (12), unknown (8), COVID-19 (2), viral infections (2), Gilbert's syndrome (1), amoxicillin-clavulanate liver injury (1), and spurious lab result (1).

Of the remaining five, only one was considered a probable DILI event due to zavegepant. The other four were assessed as possible. Overall, the liver injuries were mild with a peak median ALT of 153 U/L with a maximum of 310 U/L. There was no hyperbilirubinemia, and thus none of the cases met Hy's Law criteria.

In his review, Dr. Hayashi states that there were no clear imbalances in liver enzyme elevations between the treatment and comparator arms. However, the randomized control data were limited to single dose studies. There were modest transaminase elevations possibly attributable to zavegepant in the repeated dose safety trial. Thus, it is reasonable to conclude that intranasal zavegepant can cause mild to modest elevation in aminotransferases; if there were a propensity for patients to use the intranasal zavegepant more often than prescribed, more significant liver injury could arise post-market. However, at the dose and frequency used in the clinical trials, and as will be described on the approved labeling, the risk of DILI appears low.

Dr. Hayashi concludes that overall, the non-clinical and clinical trial data suggest a low concern for significant DILI with IN zavegepant, and he does not recommend labeling for hepatotoxicity nor routine monitoring of liver biochemistries. Because of concerns associated with this class of therapies, and the modest transaminase elevations observed in the repeated dose safety trial, enhanced pharmacovigilance for hepatotoxicity will be requested to monitor for any potential signal that may emerge in postmarketing.

Medication Overuse Headache

Although the theoretical potential for medication overuse headache (MOH) exists for zavegepant, as it is intended for the acute treatment of migraine, no data exists for this class, or any related-class, of drugs to support inclusion of a MOH warning in labeling. Drugs targeting the CGRP pathway that result in consistent daily exposures (although dosed monthly or every 3 months) are also approved for the preventive treatment of migraine. Therefore, currently, there is no empirical basis to restrict the number of acceptable monthly doses, beyond the limitations related to the available safety data (i.e., 8 attacks/month).

Suicidality and Depression

Dr. Kau has evaluated the risks of suicidality and depression using AE terms and using results of the Sheehan Suicidality Tracking Scale (S-STS) in Studies 201, 301, and 202 and concludes that there does not appear to be a signal for suicidal ideation or behavior among subjects treated with zavegepant.

Safety Conclusions

The safety profile of zavegepant is acceptable for the acute treatment of migraine with or without aura in adults. There are no safety issues that preclude approval.

Most notable in this application is the low number of SAEs overall, specifically in the controlled clinical trials. None of the reported SAEs clearly appear clearly related to zavegepant exposure. There was a cardiac related death in a subject participating in a preventive treatment of migraine study for zavegepant. This event occurred on the same day as his last reported dose of oral zavegepant 100 mg (which has similar exposure to the 10 mg intranasal dose) for which a role of zavegepant could not be definitively excluded. The case is confounded by the fact that the subject had underlying cardiovascular disease identified on autopsy. Another subject experienced an SAE of special interest, specifically a cerebrovascular accident, in the open-label safety study, but this event occurred 8 days (over 30 half-lives) following her last dose of zavegepant. Due to the lack of a temporal relationship and other confounding factors such as the identification of a PFO and hypercoagulable state, a role of zavegepant seems unlikely.

Zavegepant was also found to cause AEs such as taste disorders, nausea, nasal discomfort, vomiting, throat irritation, nasal congestion, and fatigue/somnolence. Those AEs that occurred at an incidence of 2% or greater, and that occurred more frequently than placebo, are taste disorders, nausea, nasal discomfort, and vomiting, and thus these are recommended for inclusion in labeling. None of these AEs were serious. The risks of zavegepant can be accurately conveyed with labeling.

A risk of serious hypersensitivity reactions, which is seen with several CGRP antagonists, will be described in labeling.

Labeling will limit the use of zavegepant to the treatment of no more than 8 migraines per month, consistent with the approach used in the development program.

A pregnancy registry and pregnancy outcome studies will be required. Pediatric post-marketing studies will be required to evaluate the safety and efficacy of this product in this population.

There should be enhanced pharmacovigilance of CV events, cerebrovascular events, and hepatotoxicity.

9. Advisory Committee Meeting

This application was not referred to an FDA advisory committee because it was clear that the applicant had provided substantial evidence of effectiveness from two adequate and well-controlled studies, using clinical trial designs similar to those of trials for previously approved drugs for the acute treatment of migraine. Moreover, the safety profile was deemed acceptable for the treatment of migraine, without controversial issues.

10. Pediatrics

Zavegepant was discussed at a Pediatric Review Committee (PeRC) meeting on January 24, 2023. Agreement was reached with the applicant's plan for requesting a partial waiver of clinical trials in subjects 0 to less than 6 years of age (on the basis that such studies are highly impracticable) and a post-approval deferral of such trials in subjects 6 to 17 years of age. Please refer to Section 13 of this memo for the required pediatric postmarketing studies.

11. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI)
Dr. Cara Alfaro was the primary OSI reviewer for this application and Dr. Phillip Kronstein was the Team Leader. Dr. Alfaro states that the contract research organization (CRO) and four clinical sites were inspected in support of this NDA, specifically for Studies 201 and 301. Dr. Alfaro states that the studies appear to have been conducted adequately, and the data generated by these sites and submitted by the applicant appear acceptable in support of the respective indication.

Controlled Substance Staff (CSS)
Dr. Steven Galati from CSS concluded that the nonclinical and clinical program for zavegepant did not reveal any signal for abuse potential, and therefore the CSS do not recommend this substance be scheduled under the Controlled Substances Act. Dr. Galati further recommends that prescribing information for zavegepant omit Section 9 Drug Abuse and Dependence from product labeling.

Division of Medication Error Prevention and Analysis (DMEPA)
Dr. Beverly Weitzman was the primary reviewer and Dr. Stephanie DeGraw was Team Leader for the DMEPA review. DMEPA concludes that the final agreed-upon Prescribing Information (PI), container labels, and carton labeling are acceptable.

Mr. Carlos Mena-Grillasca reviewed the proposed proprietary name, Zavzpret, and concluded that this name is acceptable.

During the IND review, DMEPA corresponded with the applicant regarding whether human factor studies would be needed to support this application because the proposed presentation of zavegepant for intranasal dosing (b) (4) Following review of the use related risk analysis data, and comparative analysis data, DMEPA determined that the risks identified are not new or unique when compared to similar marketed sprays, and that there is no difference in the intended users, intended uses, and intended use environments between (b) (4) and the proposed product. DMEPA therefore agreed that (b) (4) was an appropriate comparator. DMEPA also reviewed a comparative task analysis and determined that there were three applicant's identified task differences that impact critical administration tasks, specifically, gripping the device, tilting the head, and head position after administration. DMEPA recommended changes to the Instructions of Use to address these differences. Based on this evaluation,

DMEPA concluded that a human factor validation study was not needed to support the safe use of zavegepant as proposed by the applicant.

12. Labeling

See the final negotiated product label. Agreement was reached with the applicant on labeling.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)
The Division of Risk Management (DRISK) has determined that a REMS is not necessary for zavegepant.

Pharmacovigilance
There should be enhanced pharmacovigilance postmarketing with periodic evaluation of CV events, cerebrovascular events, and hepatotoxicity.

Postmarketing Requirements (PMRs)

PMR-1 A juvenile animal toxicology study in rat.

PMR-2 An open-label, single-dose study to evaluate the safety, tolerability, and single-dose pharmacoketics (PK) of zavegepant in patients with migraine ages 6 through 11 years.

PMR-3 A randomized, double-blind, placebo-controlled efficacy and safety study under PREA for the acute treatment of migraine with or without aura in patients ages 6 through 17 years. This study includes an initial single-blind-placebo lead-in phase to identify placebo non-responders to enroll in the efficacy portion of the trial. This efficacy study must be designed to show superiority of zavegepant over placebo.

PMR-4 A pediatric open-label, safety study under PREA to evaluate the long-term safety of zavegepant in migraine patients ages 6 to 17 years. This study should be a minimum of one year in length. 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.

PMR-5 A prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with migraine exposed to zavegepant during pregnancy with two unexposed control populations: one consisting of women with migraine who have not been exposed to zavegepant before or during pregnancy, and the other consisting of women without migraine. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-

gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

PMR-6 A pregnancy outcomes study using a different study design than provided for in PMR-4 (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small-for-gestational-age births in women exposed to zavegepant during pregnancy compared to an unexposed control population.

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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