

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212728Orig1s000

SUMMARY REVIEW

Summary Review

Date	February 26, 2020
From	Heather Fitter, MD Nick Kozauer, MD Billy Dunn, MD
Subject	Summary Review
NDA #	212728
Applicant	Biohaven
Date of Submission	June 27, 2019
PDUFA Goal Date	February 27, 2020
Proprietary Name	Nurtec ODT
Established or Proper Names	Rimegepant
Dosage Form	75 mg oral disintegrating tablet (ODT)
Applicant Proposed Indication(s)/Population(s)	Acute treatment of migraine with and without aura in adults
Applicant Proposed Dosing Regimen(s)	75 mg
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Acute treatment of migraine with and without aura in adults
Recommended Dosing Regimen(s)	75 mg

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Rimegepant is a new molecular entity (NME) developed for the acute treatment of migraine with and without aura in adults. This is the second oral calcitonin gene-related peptide (CGRP) antagonist to be reviewed in an FDA marketing application. The current application is for an oral disintegrating tablet (ODT) formulation of rimegepant, which the applicant submitted for priority review using a rare pediatric disease priority review voucher. The information from a concurrent application for a tablet formulation that was necessary to support the review of the ODT formulation was cross-referenced and also reviewed under that priority review timeline; however, the tablet application is under a standard review.

There are many FDA-approved drugs for the acute treatment of migraine with and without aura in adults, including triptans (5-HT_{1B/1D} receptor agonists), lasmiditan (5-HT_{1F} receptor agonist), ubrogepant (a CGRP antagonist), dihydroergotamine (DHE), and certain non-steroidal anti-inflammatory drugs (NSAIDs), the latter of which can be used alone or in combination with a triptan. In addition, there are over-the-counter products marketed for migraine. The use of many of the marketed prescription medications described above 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. Ubrogepant also does not include a restriction for patients with CV disease. There are currently 4 injectable monoclonal antibodies that target the CGRP system and that are indicated for the preventive treatment of migraine in patients with chronic migraine and episodic migraine. Three products (erenumab, fremanezumab, and galcanezumab) are administered subcutaneously (SC), while eptinezumab is administered intravenously (IV). The approved products targeting the CGRP system do not appear to be associated with increased CV risk.

The efficacy of rimegepant was demonstrated in three adequate and well-controlled studies. Two studies used a conventional immediate-release oral tablet, and one study used the ODT formulation. The tablet and ODT formulations were found to be bioequivalent (BE), and the data (b) (4) supportive. The studies used well-validated and clinically meaningful co-primary endpoints to establish efficacy: the proportion of patients who were pain-free and the proportion of patients who were most bothersome symptom (MBS)-free at 2 hours after dosing for the acute treatment of a migraine attack. All three studies evaluated the efficacy and safety of a single 75 mg dose of rimegepant. Rimegepant 75 mg was effective and demonstrated statistically significant superior results on both co-primary endpoints compared to placebo. The dose-response for rimegepant was relatively flat between 75-300 mg in the Phase 2 dose-finding study; therefore, only the 75 mg dose was selected for

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evaluation in Phase 3. The treatment effect size for pain freedom at 2 hours post-dose was approximately 5-10% greater than placebo (rimegepant responder rate of approximately 19-21%). The treatment effect size for MBS-freedom at 2 hours was approximately 8-12% greater than placebo (rimegepant responder rate of approximately 35-38%).

The development program did not assess the efficacy or safety of a second dose taken following a single migraine.

The safety profile of rimegepant was characterized in the three controlled efficacy studies, and a long-term open-label study with repeat dosing. Except for the efficacy study conducted with the ODT formulation, the additional controlled efficacy trials and the open-label safety study were conducted with the tablet formulation; however, as these formulations are BE, data [REDACTED] ^{(b) (4)} supportive. Overall, the safety profile was favorable, with the most common treatment emergent adverse event in the rimegepant-treated patients in the controlled clinical trials being nausea. No serious adverse event (SAE) in the controlled trials was clearly related to rimegepant use. The applicant allowed for up to daily use of rimegepant in a long-term open-label safety trial, and had sufficient safety data to support the use of up to 15 tablets of rimegepant per month.

Although a dedicated hepatotoxicity study was not done, the applicant evaluated hepatic toxicity by including a cohort of 286 patients in the open-label safety trial that took rimegepant every other day whether a migraine was present or not, and were also allowed to take rimegepant, as needed, for a migraine. No serious toxicities were identified in these trials. The common adverse event identified in clinical trials was nausea. Clinical trials included generally younger, healthy patients and effectively excluded patients with major CV disease. The data provided with this application do not support the need for CV restrictions with the use of rimegepant; however, these data are too limited to definitively establish the CV safety of rimegepant.

The risk/benefit profile of rimegepant ODT is acceptable and supports approval for the acute treatment of migraine with and without aura in adults. There is no evidence to suggest that rimegepant is more effective than other FDA-approved drugs for the acute treatment of migraine; however, rimegepant as an ODT formulation may offer a treatment alternative to some patients. Labeling will clearly convey the generally favorable safety profile demonstrated in this application. The observed increase in the incidence of nausea as compared with placebo will be noted, as will a Warning and Precaution statement regarding the potential for hypersensitivity reactions.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none">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.	Migraine is a serious and frequently disabling condition that can impact the quality of patients' lives.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>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.</p> <ul style="list-style-type: none"> • 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 United States (U.S.), thus resulting in a major impact to public health. 	
<p>Current Treatment Options</p>	<ul style="list-style-type: none"> • There are many FDA-approved therapies for acute migraine such as triptans, dihydroergotamines (DHE), lasmiditan, ubrogepant (another oral CGRP antagonist) 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. Ubrogepant does not include any CV restriction and allows for a second dose to be taken 2 hours after the initial dose. In addition, there are several over-the-counter drugs marketed for migraine. 	<p>Several classes of drugs are indicated for the acute treatment of migraine with and without aura in adults. However, many patients still do not respond adequately to these therapies.</p> <p>An additional option for the acute treatment of migraine could be desirable for patients that do not respond to the currently available treatments and/or for patients that may prefer an ODT to a conventional tablet.</p>
<p>Benefit</p>	<ul style="list-style-type: none"> • The efficacy of rimegepant was demonstrated in three adequate and well-controlled clinical studies, one study using the ODT formulation (Studies 303) and two studies using the tablet formulation (Studies 301 and 302). The studies used well-validated and clinically meaningful endpoints to establish efficacy, the proportion of patients that are pain-free (PF) at 2 hours post-dose, and most bothersome symptom (MBS)-free at 2 hours post-dose. All three studies evaluated one dose level (75 	<p>Rimegepant is effective for the acute treatment of a migraine with and without aura in adults.</p> <p>The recommended dose of rimegepant ODT for marketing will be 75 mg, with no option of a second dose within 24 hours.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons																																																		
	<p>mg rimegepant) compared to placebo. Results are summarized in the table below; comparisons between the rimegepant and placebo are highly statistically significant.</p> <table border="1" data-bbox="394 358 1270 883"> <thead> <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> </thead> <tbody> <tr> <td>Study 303</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Placebo</td> <td>10.9</td> <td></td> <td>26.8</td> <td></td> </tr> <tr> <td>Rimegepant 75 mg</td> <td>21.2</td> <td>10.8</td> <td>35.1</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>14.3</td> <td></td> <td>27.7</td> <td></td> </tr> <tr> <td>Rimegepant 75 mg</td> <td>19.2</td> <td>4.9</td> <td>36.6</td> <td>8.9</td> </tr> <tr> <td>Study 302</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Placebo</td> <td>12.0</td> <td></td> <td>25.2</td> <td></td> </tr> <tr> <td>Rimegepant 75 mg</td> <td>19.6</td> <td>7.6</td> <td>37.6</td> <td>12.4</td> </tr> </tbody> </table> <ul style="list-style-type: none"> The efficacy of a second dose to treat a single migraine when the initial dose did not yield an optimal response was not evaluated in any of the three pivotal clinical studies. 		PF at 2 hours (%)	Placebo corrected PF (%)	MBS free at 2 hours (%)	Placebo corrected MBS free (%)	Study 303					Placebo	10.9		26.8		Rimegepant 75 mg	21.2	10.8	35.1	8.3	Study 301					Placebo	14.3		27.7		Rimegepant 75 mg	19.2	4.9	36.6	8.9	Study 302					Placebo	12.0		25.2		Rimegepant 75 mg	19.6	7.6	37.6	12.4	
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<p>Risk and Risk Management</p>	<ul style="list-style-type: none"> The most common treatment emergent adverse event (TEAE) in the pooled Phase 3 controlled clinical trials of rimegepant-treated patients was nausea. There were no patients in the controlled trials that experienced a serious adverse event (SAE) that appeared to be causally related to rimegepant use. The rate of adverse dropouts was low and there was no clear pattern or adverse event (AE) that led to withdrawal during the controlled trials. Clinical trials included generally younger, healthy patients and effectively excluded patients with major CV disease. 	<p>There were no significant safety findings that would preclude approval of rimegepant. Adequate labeling and enhanced pharmacovigilance will address the identified safety issues.</p> <p>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 rimegepant.</p>																																																		

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	<ul style="list-style-type: none"> • Based on either the proposed mechanism of action or previous safety issues seen with CGRPs, safety issues of concern for rimegepant were CV effects, cerebrovascular effects, gastrointestinal effects, 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. • Hypersensitivity reactions were seen with rimegepant and while most cases were not serious, there were several that were serious but resolved with treatment. <p>Other uncertainties</p> <ul style="list-style-type: none"> • The risk of adverse outcomes in pregnancy has not been characterized. • Safety and efficacy in pediatric migraine patients has not been established. 	<p>Because the risk of adverse outcomes in pregnancy has not been characterized, and because rimegepant will be used in women of childbearing potential, a pregnancy registry and a pregnancy outcomes study will be postmarketing requirements.</p> <p>Since safety and efficacy of rimegepant in pediatric migraine patients has not been established, studies to evaluate rimegepant in pediatric migraine patients will be required under the Pediatric Research Equity Act (PREA).</p> <p>There should be enhanced pharmacovigilance with periodic evaluation of CV events, cerebrovascular events, and serious gastrointestinal events.</p>

2. Background

This review discusses the data presented by Biohaven (the applicant) in support of a new drug application (NDA) for rimegepant orally disintegrating tablets (ODT) for the acute treatment of migraine with and without aura in adults. Rimegepant is a calcitonin gene-related peptide (CGRP) receptor antagonist intended for oral 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, a 5-HT_{1F} agonist (lasmiditan), and another oral CGRP antagonist (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). Recently, three 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) and galcanezumab (Emgality) targeting the CGRP peptide.

Rimegepant is the second marketing application for a small molecule targeting CGRP. Previously, development of other small molecules in this class has been limited by the finding of serious hepatotoxicity. Therefore, the Division had discussions with the applicant about the need to thoroughly evaluate this signal in the rimegepant development program. The applicant proposed to do a dedicated double-blind hepatic safety study in which subjects would receive daily drug for three months. This study was ultimately not conducted, but instead the applicant provided results from its open-label safety study to support the hepatic safety of its product, including a cohort that took rimegepant every other day for two months.

To characterize any cardiovascular (CV) risk of this product, considering CGRP is thought to be involved in reactive vasodilatation in the face of ischemia, the Division stated that patients with CV disease should be included in studies to investigate the safety of rimegepant in this population. The Division acknowledged that assay sensitivity would be expected to be low due to the infrequent number of cardiac events that would likely be observed in the clinical

trials; however, the approved products acting on the CGRP system have not demonstrated an increase in CV risk.

The applicant provides data from three placebo-controlled efficacy trials, one study conducted with the ODT formulation and two studies conducted with an immediate-release tablet formulation, in patients with migraine with and without aura to support the efficacy of rimegepant for the acute treatment of migraine. Bioequivalence (BE) was established between the ODT and tablet formulations, allowing data from the respective trials to be mutually supportive. Study 303 (ODT study) and Studies 301 and 302 (tablet studies) evaluated a single 75 mg dose.

The current application for rimegepant ODT (NDA 212728) was reviewed on a priority review timeline because it was submitted using a rare pediatric disease priority voucher, while the application for rimegepant tablets (NDA (b) (4)) is under review on standard review timeline. The information from NDA (b) (4) that was required to support the current application (e.g., manufacturing information, efficacy findings, etc.) was cross-referenced and reviewed under the priority timeline.

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). Rimegepant is a new molecular entity that has been developed in two dosage forms, an ODT, and a conventional immediate-release tablet, each containing 75 mg of rimegepant.

Rimegepant ODT is designed to disintegrate rapidly in contact with saliva when placed on or under the tongue. This product used the proprietary “Zydis” technology in which individual tablets are produced by lyophilizing a solution or suspension containing the active ingredient and excipients in a preformed blister. The drug substance, rimegepant sulfate, is adequately characterized, the manufacturing process is adequately described, and the designated starting materials are consistent with regulatory recommendations. Two specified impurities with proposed limits above the ICH Q3A qualification threshold were adequately qualified and no mutagenic impurity risks were identified. Based on the stability data provided, the OPQ review concludes that the proposed (b) (4) retest date for drug substance stored at (b) (4) is acceptable.

Dr. Heimann reports that all facilities involved in the manufacture and testing of rimegepant sulfate and rimegepant ODT are currently acceptable.

The overall manufacturing inspection recommendation is approval. There are no significant outstanding manufacturing or facility issues and all manufacturing facilities for this application are in good standing.

The ODT formulation is considered BE to the rimegepant tablet. The adequacy of the proposed dissolution method and acceptance criteria were evaluated. Based on this evaluation,

the applicant was asked to reduce the volume of dissolution medium from (b) (4) to 500 mL, and the applicant agreed to revise the dissolution method in a changes being effected (CBE) supplement following the application's action date. The final dissolution test, with a volume of 500 mL dissolution medium, is deemed acceptable for batch release and stability testing.

OPQ recommends approval of this application for rimegepant ODT and states that this application provides adequate information to ensure that the applicant can consistently manufacture a product that is suitable for the intended population.

4. Nonclinical Pharmacology/Toxicology

The primary nonclinical reviewer for this application was Dr. David Carbone with Dr. Lois Freed performing the secondary review. A standard battery of nonclinical studies was conducted. Refer to Dr. Carbone's review of this NDA for a detailed discussion of these studies.

The following are among the key conclusions from review of the nonclinical studies:

- There were no safety concerns regarding excipients or impurities.
- There were no vasoconstrictive effects on isolated human coronary or cerebral arteries.
- Rimegepant was negative in an in vitro hERG assay.
- In the 6-month rat toxicology study, the primary toxicity identified was centrilobular vacuolation in the liver, which resolved over a recovery period. Liver vacuolation was observed at all doses (0, 5, 20, or 45 mg/kg/day) in the 6-month study; however, necrosis was only observed at the high-dose of 150 mg/kg/day in the 3-month study (and also in short-term non-GLP studies at doses greater than 100 mg/kg/day). In the 6-month study, the high-dose was identified as the no observed adverse effect level (NOAEL) and was associated with plasma AUCs of 207938-268646 ng*hr/mL.
- In the 9-month oral toxicology study in cynomolgus monkey (testing doses of 0, 5, 15, and 50 mg/kg/day), the primary toxicities were emesis and intravascular hemolysis. One high-dose male was sacrificed moribund with clinical signs and severe anemia. Based on this finding, the NOAEL for daily administration of rimegepant for 9 months was 15 mg/kg/day. Plasma exposures [Area under the Curve (AUC)] at the mid- and high-doses in the 9-month study were 3266-7110 and 61768-89178 ng*hr/mL, respectively.
- Two fertility studies in rat identified uterine atrophy at doses greater than 25 mg/kg; the NOAEL [associated with a plasma AUC on gestational day 7 (GD7) of 59400 ng*hr/mL], and decreased conception and increased pre-implantation loss at 150 mg/kg/day. There was no embryofetal toxicity in rat or rabbit.
- In a pre- and postnatal development study in rat, there were no drug effects on litter parameters or development of the offspring; however, because the male mating index, male and female fertility indices, and female pregnancy rates in all groups following mating were below the lower limit for the conducting laboratory's historical range, the pre- and postnatal development study did not adequately assess mating and fertility in the offspring.

- Rimegepant was negative in Ames, in vitro chromosomal aberration, and in vivo rat micronucleus assays, and was negative for tumor formation in 6-month and 2-year carcinogenicity studies.

Drs. Carbone and Freed have determined that although toxicities of concern were observed in rat and monkey, they were associated with plasma AUCs substantially higher than that in the maximum recommended human dose (MRHD) of 75 mg/day (3729 ng*hr/mL). Similarly, the NOAEL dose for impairment of fertility or early embryonic development resulted in exposures (based on plasma AUC on GD7) approximately 15 times that in humans at the MRHD.

Drs. Carbone and Freed conclude that the nonclinical data are adequate to support approval of the NDA; however, the completed pre- and postnatal development study of rimegepant in rats was inadequate. Therefore, they are recommending a pre- and postnatal development study in rat as a post-marketing requirement (PMR) to address these deficiencies and a PMR for a juvenile animal toxicology study to support clinical development in pediatric patients under the Pediatric Research Equity Act (PREA).

5. Clinical Pharmacology

The primary reviewer for the Office of Clinical Pharmacology (OCP) review was Dr. Girish Bende. Dr. Sreedharan Sabarinath was the team leader. The OCP review states that the clinical pharmacology information included in this NDA support approval of the 75 mg dose, with a maximum daily dose of 75 mg.

The OCP review has made conclusions regarding the ODT and tablet formulations, which are discussed below; however, as mentioned previously, the current application is only for the ODT formulation.

In addition to the three randomized, double-blind, placebo-controlled safety and efficacy studies, two studies using the tablet formulation and one study using the ODT, this application also included 18 Phase 1 clinical studies and one Phase 2 study.

The formulations used in the clinical efficacy trials were the same as the to-be-marketed formulations; therefore, no pharmacokinetic (PK) bridging studies were required. The applicant demonstrated BE between the to-be-marketed tablet and ODT.

Mechanism of Action

Dr. Bende states that rimegepant is a human CGRP receptor antagonist. CGRP and its receptors are expressed in regions of the nervous system associated with migraine pathophysiology. 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.

Absorption

The mean absolute bioavailability of rimegepant following oral administration is 64%. The relative bioavailability study demonstrated that the bioavailability of rimegepant ODT is comparable to that with the tablet formulation. The median T_{max} of the ODT and tablet formulations were 1.5 hours and 1.9 hours, respectively. Following administration of both the tablet or ODT under fed conditions, the rate and extent of absorption of rimegepant was

reduced compared to that observed under fasting conditions. For the ODT, administered sublingually, the time to maximum plasma concentration was delayed by 1 hour, peak concentration was reduced by 42%, and total exposure was reduced by 32%. For ODT administered supra-lingually, these parameters were similar (time to maximum plasma concentration delayed by 1 hour, peak concentration reduced by 53%, and total exposure was reduced by 38%). For the tablet, time to maximum rimegepant plasma concentration was delayed by 1 hour, peak concentration was reduced by 33%, and total exposure was reduced by 30%.

The clinical efficacy studies were conducted without regard to food, and no information on the fasted/fed state during efficacy assessments were collected; therefore, the impact of the food effect on the efficacy of rimegepant could not be assessed. The OCP review does not recommend dosing adjustments with regard to food (a recommendation that would also be impractical for an acute treatment for migraine).

Distribution

Plasma protein binding of rimegepant is approximately 96%. The mean apparent central volume of distribution of rimegepant is approximately 120 L at steady state.

Metabolism and Elimination

Metabolism of rimegepant is primarily mediated by CYP3A4 and to a lesser extent by CYP2C9. Rimegepant is primarily eliminated in an unchanged form (77%) with no major metabolites detected in plasma. Hydroxylation, forming mono- and bis-hydroxylated metabolites, was the most significant biotransformation pathway. Other metabolites excreted were glucuronides. The average elimination half-life is 1 hour. The mean plasma clearance is approximately 9.3 L/h. Following a single oral dose of rimegepant, the primary route of elimination is through the biliary/fecal pathway and the urinary pathway is a minor route of elimination.

Special Populations/Intrinsic Factors

Dr. Bende reports that the PK of rimegepant in subjects with mild, moderate, or severe renal impairment had no clinically meaningful differences in PK compared to subjects with normal renal function. No dose or dosing frequency adjustment is required in patients with renal impairment. Patients with end-stage renal disease (ESRD) should avoid use of rimegepant.

The PK of rimegepant in subjects with mild or moderate hepatic impairment demonstrated no clinically meaningful differences from the PK of rimegepant in subjects with normal hepatic function. Higher exposures of rimegepant (2-fold increases) were seen in patients with severe hepatic impairment. Dr. Bende recommends avoiding use of rimegepant in patients with severe hepatic impairment.

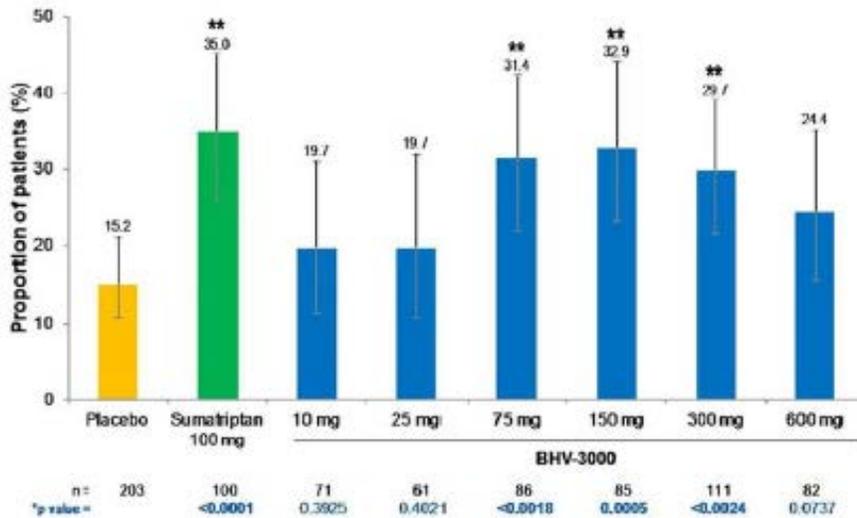
Body weight, gender, race, and age, did not have a clinically relevant effect on the exposure of rimegepant.

Dosing

To inform dosing, the applicant conducted a randomized, double-blind, placebo-controlled, dose-ranging study (CN170003). Patients were randomized to one of 8 arms: placebo,

rimegepant (10 mg, 25 mg, 75 mg, 150 mg, 300 mg, or 600 mg), or sumatriptan (100 mg). The primary outcome was pain freedom at 2 hours post-dose. Figure 1 below demonstrates the relatively flat dose-response between rimegepant 75 mg and 300 mg, with no apparent efficacy at rimegepant 25 mg; therefore, the applicant selected only the 75 mg dose to evaluate in its efficacy trials.

Figure 1: Study CN170003- Proportion of Patients with Pain Freedom at 2 hours (source: Dr. Bende's review Figure 3-1 from applicant's analysis)



Drug-Drug Interactions

There was an increase in exposure with the concomitant administration of 75 mg rimegepant and strong inhibitors of CYP3A4. Therefore, Dr. Bende recommends avoiding concomitant administration of rimegepant with a strong inhibitor of CYP3A4. No dedicated drug-drug interaction study was conducted to assess the effect of concomitant administration of moderate or weak inhibitors of CYP3A4 on the PK of rimegepant. No dose adjustment is recommended with a moderate inhibitor of CYP3A4; however, it is recommended to avoid another dose of rimegepant within 48 hours when it is used with a moderate inhibitor of CYP3A4.

When rimegepant 75 mg was administered with a strong inducer of CYP3A4, there were reduced exposures of rimegepant that may lead to loss of efficacy (80% in AUC, 64% C_{max}). Therefore, Dr. Bende recommends avoiding concomitant administration of rimegepant with a strong inducer of CYP3A4. No dedicated drug-drug interaction study was conducted to assess the effect of concomitant use of moderate or weak inducers of CYP3A4 on the PK of rimegepant. Dr. Bende states that concomitant administration of rimegepant with moderate inducers of CYP3A4 may result in decreased rimegepant exposures, and may reduce efficacy. The dose finding studies suggest that lower doses are not effective; therefore, Dr. Bende recommends avoiding concomitant administration of moderate inducers of CYP3A4 with rimegepant. No change in the dose or dosing regimen is recommended with weak inducers of CYP3A4.

No dose adjustment is recommended with concomitant administration of rimegepant with an inhibitor of CYP2C9.

Rimegepant is a substrate of P-gp and BCRP based on the in vitro studies. Therefore, concomitant administration of inhibitors of P-gp or BCRP may increase the exposure of rimegepant. No dedicated drug-drug interaction study was done to assess their effects on the PK of rimegepant. Since there is limited safety information for doses above 75 mg, and there may be concerns about increased exposures, Dr. Bende recommends that concomitant administration of rimegepant with an inhibitor of P-gp or BCRP should be avoided.

OCP recommends approval of this application for 75 mg dose of rimegepant, with a maximum dose of 75 mg in a 24-hour period.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical - Efficacy

Dr. Laura Jawidzik conducted the clinical efficacy review for this application. Dr. Joanne Liu conducted the biometrics review and Dr. Kun Jin was the biometrics team leader.

The applicant conducted three placebo-controlled efficacy trials (Table 1) in adult migraine patients with and without aura: Study 303, 301, and 302. Note that Study 303 is listed first, as it evaluated the ODT formulation that is the subject of the current application; however, a review of the efficacy from both formulations was necessary to support a conclusion regarding the efficacy of rimegepant.

Table 1: Clinical Efficacy Studies

	Population	Primary Endpoints	Treatment Duration	Doses	Sample Size
Study 303	Adults with migraine with or without aura	Pain freedom at 2 hours; freedom from MBS	Single attack	75 mg ODT orally	1351
Study 301	Adults with migraine with or without aura	Pain freedom at 2 hours; freedom from MBS	Single attack	75 mg tablet orally	1084
Study 302	Adults with migraine with or without aura	Pain freedom at 2 hours; freedom from MBS	Single attack	75 mg tablet orally	1072

Studies 303, 301, and 302

The three efficacy studies were designed identically, with the exception that Study 303 had some differences in the pre-specified order of testing secondary endpoints, described below.

These studies were designed as multicenter, randomized, double-blind, placebo-controlled, parallel-group studies in adult patients with migraine to evaluate the efficacy of rimegepant in the acute treatment of migraine with and without aura. Patients were randomized in a 1:1 ratio to receive either rimegepant 75 mg or placebo. Patients were instructed to treat a qualifying migraine within 45 days of randomization, and were instructed not to take a second dose of the investigational product (IP). Patients who completed the double-blind treatment period were offered enrollment into an open-label extension study.

Patients eligible for enrollment were adults 18-75 years of age with at least a one-year history of migraine with or without aura. Patients had to be diagnosed with migraine before the age of 50 years and have a history of less than 15 headache days/month in each of the 3 months before screening. Patients with a history of uncontrolled, unstable, or recently diagnosed CV disease including ischemic heart disease, coronary artery disease, or cerebral ischemia were excluded.

The co-primary endpoints used to establish efficacy were the proportion of patients who were headache pain-free at 2 hours, and the proportion of patients who were most bothersome symptom (MBS)-free at 2 hours, following dosing of IP. Pain freedom was defined as the reduction in headache severity from moderate or severe pain at baseline to no pain at two hours after dosing. The MBS was defined as either nausea, phonophobia, or photophobia, and was to be determined prospectively by the patient at the time of a qualifying migraine attack but before administration of study drug. The statistical analysis plan specified that both co-primary endpoints would have to be statistically significant in favor of rimegepant in order to consider the study supportive of a treatment effect.

For Study 303, the protocol included the following extensive list of secondary endpoints that were sequentially controlled for Type I error in the order presented here:

- Pain relief at 2 hours
- Proportion of patients able to work or function normally at 2 hours
- Sustained pain relief (SPR) from 2 to 24 hours
- Sustained freedom from MBS from 2 to 24 hours
- Probability of requiring rescue medication within 24 hours
- Sustained normal functioning from 2 to 24 hours
- SPR from 2 to 48 hours
- Sustained freedom from MBS from 2 to 48 hours
- Sustained normal functioning from 2 to 48 hours
- Photophobia freedom at 2 hours
- Functional disability at 90 minutes
- Pain relief at 90 minutes
- Sustained pain freedom (SPF) from 2 to 24 hours
- MBS freedom at 90 minutes
- Pain freedom at 90 minutes
- Phonophobia freedom at 2 hours

- SPF from 2 to 48 hours
- Pain relief at 60 minutes
- Functional disability at 60 minutes
- Nausea freedom at 2 hours
- Pain relapse from 2 to 48 hours

For Studies 301 and 302, the protocols included the following secondary endpoints that were sequentially controlled for Type I error in the order presented here:

- SPF from 2-24 hours
- Photophobia freedom at 2 hours
- Phonophobia freedom at 2 hours
- Nausea freedom at 2 hours
- Probability of requiring rescue medication within 24 hours
- SPF from 2-48 hours
- SPR form 2-24 hours
- SPR from 2-48 hours
- Proportion of patients able to work or function normally at 2 hours

The efficacy analyses were conducted on the modified intent to treat (mITT) population defined as all randomized patients who received at least 1 dose of IP and provided at least one efficacy measurement. For the two co-primary endpoints, the between group difference in the percentage of pain-free subjects or MBS-free patients at 2 hours post-dose was assessed by using the Cochran-Mantel Haenszel (CMH) weights, stratified by preventive migraine medication use. Patients that took rescue medication were considered failures for any efficacy evaluations at the time, or following the time, of the rescue medication. Patients that recorded their MBS after taking the IP, or who did not provide an MBS, were considered failures for the analysis of MBS. Missing data at 2 hours were imputed as failures. The multiplicity adjustment method was pre-specified and adequate. If the primary endpoint tests were both significant, then the secondary endpoints were evaluated using a fixed-sequence hierarchical gate-keeping procedure, with each test in the hierarchy conducted at $p = 0.05$. If one analysis in the hierarchy was not statistically significant, then all subsequent analyses would be exploratory.

Results

Studies 303, 301, and 302

The median age of the patients in all three trials was 39-40 years. Eighty-five to 89% of patients were female, and 73 to 82% 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 over the past 3 months was 4, approximately 28-35% of patients experienced migraine both with and without aura, and 15-

17% of patients used concomitant preventive migraine medications. Approximately 2-3% of patients were 65 years of age or older.

Co-primary Endpoints

Table 2 presents the results of the primary efficacy analyses for Studies 303, 301, and 302.

Table 2: Studies 303, 301, and 302- Primary Efficacy Endpoint Results (source: modified from Dr. Jawidzik's review Table 80 and Dr. Liu's review*)

	303		301		302	
	75 mg	PBO	75 mg	PBO	75 mg	PBO
Pain Freedom at 2 hours						
n/N	142/669	74/682	104/543	77/541	105/537	64/535
%Responders	21.2	10.9	19.2	14.3	19.6	12.0
Difference from placebo	10.4		5.0		7.6	
p-value	<0.0001		0.0298		0.0006	
Absence of from MBS						
n/N	235/669		199/543	150/541	202/537	135/535
%Responders	35.1	26.8	36.6	27.7	37.6	25.2
Difference from placebo	8.3		8.9		12.4	
p-value	0.0009		0.0016		<0.0001	

*Dr. Liu's NDA 212728 review-Table 12 and NDA (b) (4) review-Table 9 and 23)

Drs. Jawidzik and Liu both conclude that treatment with rimegepant resulted in statistically significant increases in the proportion of patients reporting pain freedom at 2 hours post-dose and MBS freedom at 2 hours post-dose, as compared to placebo, for the 75 mg dose in Studies 303, 301, and 302.

Missing data for the pain freedom and MBS endpoints at 2 hours post-dose ranged from approximately 3-5% for Study 303, to 4-7% for Study 301, and 3% for Study 302. Sensitivity analyses were conducted in which missing data at 2 hours post-dose were imputed using the last available value (LAV). Additional sensitivity analyses used only data from completed cases (data present at baseline and 2 hours post-dose). Results from both sensitivity analyses were consistent with the pre-specified primary efficacy analysis.

Dr. Liu notes that eDiary software issues were reported at the initiation of Studies 301 and 302. Approximately one month after the studies began there were errors in the functioning of the e-Diary including inadequate alarms to signal patients to enter data, failures to click "ok" resulting in lost data in certain cases, and cases in which some patients were automatically logged out. Overall, these occurrences were limited (3-7% missing data for the primary endpoints in each trial, with most cases involving datapoints after the 2 hour post-dose timepoint). Dr. Liu performed various sensitivity analyses (discussed in detail in her review) to evaluate the effect of this e-Diary malfunction on the study results, and determined that the

results of the sensitivity analyses were consistent with the results of the pre-specified primary efficacy analysis.

Secondary Endpoints

The secondary endpoints for each trial were hierarchically tested to control for Type I error, as described above. There was significant overlap with respect to the clinical information provided by these endpoints. Of the endpoints tested, the following were determined to be the most informative and suitable for inclusion into labeling, and therefore the focus of the review team with respect to confirming the applicant's results:

- Pain relief at 2 hours
- SPF from 2-48 hours
- Proportion of patients using rescue medication from 2-24 hours
- Proportion of patients able to function normally at 2 hours

Refer to Dr. Jawidzik's review for a detailed description of the results of the analyses for the other key secondary endpoints.

In Study 303, all the key secondary endpoints that were included in the prespecified plan to control for Type I error were statistically significant in favor of treatment, except freedom from nausea at 2 hours and pain relapse from 2-48 hours. In Studies 301 and 302, statistical significance in favor of treatment was demonstrated on pain relief at 2 hours, photophobia freedom at 2 hours, and phonophobia freedom at 2 hours. The next endpoint in the hierarchy, freedom from nausea at 2 hours, was not statistically significant; therefore, formal testing for statistical significance stopped after this endpoint. The subsequent endpoints of sustained pain freedom at 48 hours, use of rescue medication, and functional disability at 2 hours were nominally significant.

Refer to Table 3, below, for the results of the analyses of the secondary efficacy endpoints to be included in labeling.

Table 3 Studies 303, 301 and 302: Results for Secondary Endpoints (source: modified from Dr. Jawidzik clinical review Tables 12, 23 and Dr. Liu's review*)

	Study 303		Study 301		Study 302	
	75 mg N=669	Placebo N=682	75 mg N=543	Placebo N=541	75 mg N=537	Placebo N=535
Pain relief at 2 hours						
Responders, n (%)	397(59.3)	295 (43.3)	304 (56)	247 (45.7)	312 (58.1)	229 (42.8)
Difference from placebo (%)	16.0		10.3		15.3	
p-value	<0.0001		<0.0006		<0.0001	
Sustained Pain Freedom at 48 Hours						
Responders, n (%)	90 (13.5)	37 (5.4)	63 (11.6)	39 (7.2)	53 (9.9)	32 (6.0)
Difference from placebo (%)	8.0		4.4		3.9	
p-value	<0.0001		0.013**		0.018**	
Use of Rescue Medication 2-24 hours						
Responders, n (%)	95 (14.2)	199 (29.2)	111 (20.4)	172 (31.8)	113 (21)	198 (37)
Difference from placebo (%)	-15.0		-11.3		-16	
p-value	<0.0001		<0.0001**		<0.0001**	
Percentage of Patients Reporting Normal Function at 2 Hours^a						
Responders, n (%)	255 (38.1)	176 (25.8)	181 (33.3)	118 (21.8)	175 (32.6)	125 (23.4)
Difference from placebo (%)	12.3	14.4	11.5		9.2	
p-value	<0.0001		<0.0001**		0.0007**	

*The tables referred to from Dr. Liu's review come from two review, the review for NDA 212728 (Tables 13, 14, 15, and 16) and the review for NDA (b) (4) (Tables 16,17,18, 19, 30, 31, 32 and 33).

**nominally significant

^aThe measurement of the percentage of patients reporting normal function at two hours was derived from a single item questionnaire, asking patients to select one response on a 4-point scale; normal function, mild impairment, severe impairment, or required bedrest.

Efficacy by Subgroups

Dr. Liu performed analyses of the treatment effect across subgroups for Studies 303, 301, and 302, and concludes that the efficacy findings observed in the primary efficacy analyses appeared to be similar across all subgroups (age, gender, weight, and race); however, no definitive conclusions can be made based on the small sample sizes for these comparisons.

Efficacy Conclusions

The applicant has provided substantial evidence of effectiveness of rimegepant based on the results from three adequate and well-controlled investigations, one study conducted with the

rimegepant ODT formulation (Study 303) and two studies conducted with the rimegepant tablet formulation (Study 301 and 302). All three studies were conducted in patients with migraine with and without aura and demonstrated significant increases in the proportion of patients who were pain-free at 2 hours post-dose and MBS-free at 2 hours post-dose in the rimegepant 75 mg group, as compared to placebo. The applicant chose to study only a single dose in its efficacy trials. The analyses of the trials' secondary endpoints were supportive of the primary efficacy analyses. The 75 mg dose is effective and should be approved. The studies did not include an option for a second dose to treat a single migraine in the pivotal trials, so the efficacy of a second dose on the day of the treated migraine was not established.

The current application, conducted under a priority review given the applicant's use of a rare pediatric disease priority review voucher, is only for the ODT formulation, as the complete review of the application for the tablet formulation (e.g., manufacturing considerations) is ongoing; however, the efficacy data from the tablet formulation and ODT formulation have been reviewed (b) (4)

8. Safety

Dr. Laura Jawidzik conducted the clinical safety review of this application.

As discussed by Dr. Jawidzik, the overall exposure to rimegepant exceeds the minimum number of patients recommended by the International Council for Harmonization (ICH) E1 Guideline for chronically administered medications. She reports that 3,397 patients were exposed to at least one dose of rimegepant, of which 1,857 were exposed in the controlled clinical trials. When considering exposure to the dose of rimegepant proposed for marketing (75 mg), 1,131 patients treated at least 2 migraines per month for at least 6 months and 863 treated at least 2 migraines per month for 12 months.

Note that the tablet formulation was used in the open-label, long-term safety study; however, given the established BE between the ODT and tablet formulations, the tablet data are capable of informing the safety profile of the ODT.

The applicant suggests that prescribing information allow for dosing of 75 mg up to daily. Following Dr. Jawidzik's review of the number of patients with exposure data up to 1 year taking frequent dosing in a month, she concludes that there is only adequate exposure to support dosing up to 15 days/month, but not daily dosing. Although a handful of patients did take rimegepant more frequently, these numbers were too small to allow for any meaningful conclusions to be drawn regarding efficacy with such use.

Dr. Jawidzik notes that this development program allowed patients 18 years of age and older to enroll, and that this safety database includes patients up to age 84; however, only a small percentage of patients were 65 years of age or older (3%).

Due to findings related to other CGRP antagonists in development or to the presumed

mechanism of action of CGRP in terms of its action to allow for compensatory vasodilatation in the face of ischemia, safety signals of concern for this application have been identified as CV events, cerebrovascular events, hepatotoxicity, and gastrointestinal events. Regarding her evaluation of these safety issues, Dr. Jawidzik notes that the migraine efficacy studies excluded patients with hepatic disease, unstable angina, myocardial infarction, TIA, and stroke, within 6 months of the study, in addition to patients with CV disease, cerebral ischemia, or significant neurological disorders. She suggests that this may limit the generalizability of the safety data to the larger population when considering that the postmarketing migraine population may be much less restrictive.

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

Deaths

There were no deaths in the development program for rimegepant.

Serious Adverse Events (SAEs)

Dr. Jawidzik notes that in the controlled clinical trials, there were 4 SAEs reported by rimegepant-treated patients, and 3 SAEs reported in patients taking placebo. No SAEs occurred in more than 1 patient and none of these SAEs appear to be related to rimegepant.

In the open-label study, Dr. Jawidzik notes that there were 66 SAEs experienced by 56 patients (out of 1,798 patients in the pool) and she describes some cases in detail in her review. There were several cases in which she concludes that a relationship to rimegepant cannot be ruled out, described briefly below:

1. A 46-year-old female developed an aortic dissection approximately 15 weeks into the study but 5 days after taking her last dose of rimegepant. She had been taking approximately 5-7 doses of rimegepant a month starting in (b) (6). The patient was also noted to have an elevated blood pressure at week 12 (150/105). Dr. Jawidzik notes that the elevated blood pressure may have been related to study drug, and an elevated blood pressure is a risk factor for aortic dissection. However, the patient was also a smoker, and smoking is a known risk factor for aortic dissection.
2. A 42-year-old female developed dyspnea, and was found to have bilateral lower lobe pulmonary emboli. This patient had a family history of deep venous thrombosis (DVT), although she had never had a DVT. Dr. Jawidzik notes that there were 5 additional cases of young women developing thrombosis on rimegepant, although these other cases were also confounded by either the use of oral contraceptives, or a previous history of thrombosis.
3. A 54-year-old female with Crohn's disease experienced abdominal pain with watery diarrhea and rectal bleeding. Following a colonoscopy with a biopsy, a diagnosis of ischemic colitis was made. This patient had taken an average of 11 tablets per 4-week period while in the study for approximately 15 weeks. Her last dose of rimegepant was the day prior to her emergency room visit.

4. A 54-year-old female who had a history of recurrent constipation reported adverse events of ulcerative colitis, gastritis, and colonic inertia. She took her first dose (b) (6) and reported ulcerative colitis from (b) (6) through (b) (6). She then experienced gastritis from the end of (b) (6) to the end of (b) (6). She continued on rimegepant and experienced the event of colonic inertia in (b) (6). This patient had been taking rimegepant for 19 out of 30 days prior and her last dose prior to the event of colonic inertia was 2 days prior. In early (b) (6) the patient was hospitalized and underwent a total abdominal colectomy with ileorectal anastomosis. She continued in the study and took her last dose of rimegepant on (b) (6). Dr. Jawidzik reports that there is biological plausibility that CGRP antagonism with rimegepant had a role in this more serious outcome by exacerbating the patient's pre-existing gastrointestinal motility problems.

Although a contribution of rimegepant cannot be excluded for these cases, they were also all confounded, which precludes the establishment of any clear association with treatment.

Discontinuations

In the controlled efficacy trials, there were no AEs leading to discontinuations. In the open-label, long-term safety study, there were 72 AEs reported that resulted in drug withdrawal. The most frequent AEs leading to drug withdrawal were the following: dizziness (5), depression (3), suicidal ideation (3), and AST/ALT elevation (3).

In addition, Dr. Jawidzik reports that there were four cases of hypersensitivity, of which one seemed clearly related to rimegepant. Two of the cases had alternative causes, and the remaining patient had further adverse events related to hypersensitivity with additional doses, but the relationship to rimegepant in this case is unclear.

Treatment Emergent Adverse Events (TEAEs)

Tables 4 and 5, modified from Dr. Jawidzik's review, summarizes the most common TEAEs from the controlled trials. These tables include several different approaches to grouping related terms.

Table 4: Studies 303, 301, and 302: TEAEs in the Double-Blind Treatment Period (source: Dr. Jawidzik's review modified from Table 58)

	Placebo N=1782	75 mg N=1771	Risk Difference (with rounding)	Relative Risk
Dyspepsia, N/V, epigastric pain	20 (1.1)	31 (1.8)	1	1.6
N/V	18 (1.0)	28 (1.6)	1	1.6
Nausea	14 (0.8)	26 (1.5)	1	1.9
Abdominal pain, dyspepsia*	4 (0.2)	16 (0.9)	1	4.5
Abdominal pain, distention**	2 (0.1)	12 (0.7)	1	7
Somnolence, fatigue, sedation	6 (0.3)	10 (0.6)	0	2

*Includes the following PTs: gastrointestinal pain, dyspepsia, abdominal pain, abdominal distention, and abdominal discomfort

**Includes the following PTs: abdominal pain, abdominal distension, and abdominal discomfort.

Table 5: Study 303: TEAEs (source: Dr. Jawidzik's review modified from Table 59)

	Placebo N=693	75 mg N=682
Dyspepsia, N/V, epigastric pain	7 (1.0)	15 (2.2)
UTI	11 (1.6)	14 (2.1)
Nausea/vomiting	6 (0.9)	13 (1.9)
Nausea	3 (0.4)	11 (1.6)
URI, cold, flu-like illness	4 (0.6)	11 (1.6)

Laboratory Findings

Dr. Jawidzik did not find clinically meaningful differences in the controlled trials between rimegepant and placebo in mean changes from baseline for the hematology, chemistry, and urinalysis results.

Vital Signs

Dr. Jawidzik reports that rimegepant did not appear to cause any clinically meaningful changes in mean systolic blood pressure (SBP), diastolic blood pressure (DBP), temperature, respiratory rate, or weight. In addition, an outlier analysis for SBP, DBP, and heart rate (HR) did not reveal any imbalances between rimegepant and placebo. Dr. Jawidzik reviewed the single ascending dose (SAD) study, in which doses from 75 mg to 1500 mg were

administered, and the multiple ascending dose study, in which doses from 75 mg to 600 mg were administered, and she did not identify any clear pattern for mean change from baseline in SBP or DBP for the marketed dose. She did identify a trend in the mean changes in SBP at the 300 mg dose in the SAD trial in which the SBP was elevated and remained elevated until 12 hours post-dose.

Electrocardiogram (ECG)

Dr. Jawidzik found no clinically significant changes from baseline in mean HR, PR interval, QRS, or QTcF, as compared to placebo in the controlled clinical trials.

Dr. Jawidzik reports that the applicant conducted a thorough QT (TQT) study (Study BHV3000-109) which was reviewed by the Interdisciplinary Review Team for QT Studies (QT-IRT). They found no significant QTc prolongation effect with the use of a single dose of 300 mg of rimegepant. They note that this dose covers the worst-case exposure scenario (i.e., severe hepatic impairment). The team has proposed the following language to be included in product labeling: “At a dose four times the recommended dose (75 mg), rimegepant does not prolong the QT interval to any clinically relevant extent.”

Cardiovascular Risk

Dr. Jawidzik did not identify any potential CV or cerebrovascular safety concerns in regard to toxicity associated with the use of rimegepant, noting that her review is limited in this respect, as the population studied was primarily young and healthy. The applicant included some patients over the age of 65 in the studies; however, the overall presence of CV, cerebrovascular, and peripheral vascular disease was low.

Dr. Jawidzik concludes that the current database does not support an increased CV risk with rimegepant and that labeling should not include CV restrictions. However, these data are also insufficient to definitively establish the CV safety of rimegepant, and enhanced pharmacovigilance for CV and cerebrovascular events in the postmarket setting will be required.

Hepatotoxicity

In order to evaluate the hepatic risk of rimegepant, the applicant attempted to enrich the long-term, open-label study (Study 201) with patients who were likely to use rimegepant frequently. In addition, the applicant included a treatment arm of patients in the open-label study who took rimegepant every other day for 12 weeks regardless of whether the patient had a migraine. Patients in this treatment arm could take additional doses, as needed, on those days when the patient experienced a migraine. A total of 286 patients were treated with rimegepant every other day in Study 201. Of these patients, there was one patient that had an ALT greater than 3x the upper limit of normal (ULN) with a total bilirubin (TBili) greater than 2x ULN. This case did not meet criteria for Hy’s Law, however, as the patient had an alternative cause for these elevations and the elevations did not occur simultaneously. There was an additional case in Study 201 that was coded as drug-induced liver injury. Dr. Jawidzik reports that both of these cases did not appear to be related to rimegepant as both patients were taking other medications known to be hepatotoxic. Refer to Dr. Jawidzik’s review for detailed discussions of these cases.

Tables 6 and 7, reproduced based on Dr. Jawidzik's review, summarize the hepatic TEAEs and an outlier analysis for elevations in ALT, AST, and total bilirubin, respectively.

Table 6: Studies 303, 301, and 302: Hepatic TEAEs (source: Dr. Jawidzik's review Table 77)

Preferred Term	Placebo N=1782 n (%)	75 mg N=1771 n(%)
ALT increased	2 (0.1)	2 (0.1)
AST increased	0	2 (0.1)
Bilirubin increased	1 (0.1)	1 (0.1)
LFT increased	3 (0.2)	2 (0.1)
Hyperbilirubinemia	0	1 (0.1)

Table 7: Studies 303, 301 and 302: Post Baseline Elevations in AST, ALT and Total Bilirubin (source: Dr. Jawidzik's review Table 78)

	Placebo N=1782 n(%)	75 mg N=1771 n(%)
AST		
≥3x ULN	0	2 (0.1)
≥5x ULN	0	1 (0.1)
≥10x ULN	0	0
ALT		
≥3x ULN	2 (0.1)	1 (0.1)
≥5x ULN	0	0
≥10x ULN	0	0
TBili (mg/dl)		
≥1.5xULN	2 (0.1)	3 (0.2)
≥ 2xULN	1 (0.1)	0

Overall, the data provided in this application do not demonstrate a hepatotoxic signal in the rimegepant safety database.

Gastrointestinal Toxicity

Constipation has been identified as a safety signal of interest due to the description in the literature of the role of CGRP in gastric motility. Although there was no imbalance compared to placebo in the rates of development of constipation during the controlled trials, there were two cases of constipation and a case of ischemic colitis that resulted in withdrawal from rimegepant. While these cases were confounded and not convincing enough to include in product labeling, they support a recommendation to have enhanced pharmacovigilance for

gastrointestinal events in the postmarket setting given the biological plausibility. In addition, nausea was the most common TEAE in rimegepant patients and abdominal distension and dyspepsia occurred at a higher incidence in the rimegepant group as compared to placebo, although the rates were low in both groups.

Medication Overuse Headache

Although the theoretical potential for medication overuse headache (MOH) exists for rimegepant, as it is intended for the acute treatment of migraine, no data exist for this class or any related class of drugs to support inclusion of an 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 based on previous limits set to avoid medication overuse headaches. The data provided by the applicant support the use of rimegepant up to 15 days a month and this information will be included in labeling.

Suicidality and Depression

Dr. Jawidzik has evaluated the risks of suicidality and depression using AE terms and using results of the Sheehan Suicidality Tracking Scale (S-STTS) used in Studies 303, 301, and 302, and concludes that there does not appear to be a signal for suicidal ideation or behavior among patients treated with rimegepant.

Safety Conclusions

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

None of the reported SAEs in the controlled portion of the clinical trials appear related to rimegepant use.

Hypersensitivity was identified and while most cases were not serious, there were several that were and required treatment to terminate the reaction. There will be a Warning and Precaution in the prescribing information regarding the risk of hypersensitivity.

Rimegepant ODT was also found to cause the common AE of nausea, a risk that can be accurately conveyed with labeling.

Labeling will limit the use of rimegepant to 15 days per month, based on safety data provided for patients using up to 15 doses/month through 1 year. The number of patients with consistent use of rimegepant beyond 15 days/month is too limited to draw any conclusions about safety.

A pregnancy registry and pregnancy outcome studies will be required.

There will be enhanced pharmacovigilance of CV events, cerebrovascular events, and serious gastrointestinal events.

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 three 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.

10. Pediatrics

Rimegepant was discussed at a Pediatric Review Committee (PeRC) meeting on January 28, 2020. Agreement was reached with the applicant's plan for requesting a partial waiver of clinical trials in patients 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 patients 6 to 17 years of age. Please refer to Section 14 of this memo for the required pediatric postmarketing studies.

11. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI)

Dr. Cheryl Grandinetti was the primary OSI reviewer for this application and Dr. Phillip Kronstein was the team leader. Dr. Grandinetti states that six clinical sites and the study applicant, Biohaven Pharmaceuticals, were inspected in support of NDA 212728 (rimegepant ODT).

Dr. Grandinetti reports that the inspection of Dr. Brandes' site (Site 002) for Protocol BHV3000-303 found significant data integrity issues and concerns related to good clinical practice (GCP) noncompliance, including, but not limited to, a lack of source documents necessary to verify the study data collected at the site. The applicant informed the Division of this noncompliance and conducted a sensitivity analysis on the primary and key secondary endpoints removing this site from the primary analysis and submitted this analysis to the NDA. These results were consistent with the prespecified primary analysis results.

The inspection of the sponsor identified issues with the electronic patient-reported outcome (ePRO) devices used during the trial, including design and validation issues (e.g., inadequate user acceptance testing (UAT) of the ePRO devices) and insufficient training and retraining of all patients and study personnel on the use of the ePRO devices. These issues contributed to a number of missing post-migraine assessments but were limited in scope due to the applicant's centralized monitoring efforts. It appears that the ePRO device software deficiencies were identified and resolved quickly.

Notwithstanding these observations, the studies appear to have been conducted adequately. The study data, including the primary efficacy endpoint data for the three protocols (303, 301, and 302), otherwise appear acceptable [REDACTED] (b) (4).

Controlled Substance Staff (CSS)

Dr. Shalini Bansil was the primary CSS reviewer and Dr. Edward Hawkins was the team

leader. Dr. Bansil reviewed the nonclinical and clinical abuse-related data submitted in the application and concludes that rimegepant does not have abuse potential and should not be scheduled under the Controlled Substances Act. In addition, Dr. Bansil notes that inclusion of Section 9 for Drug Abuse and Dependence is not required in the prescribing information.

Division of Medication Error Prevention and Analysis (DMEPA)

Dr. Celeste Karpow was the primary reviewer and Dr. Briana Rider was the team leader for the DMEPA review. DMEPA concludes that the final agreed-upon prescribing information and carton and container labeling are acceptable.

Dr. Chad Morris reviewed the proposed proprietary name, Nurtec ODT (NDA 212728), and concluded that it is acceptable.

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 (DRM) has determined that a REMS is not necessary for rimegepant.

Pharmacovigilance

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

Postmarketing Requirements (PMRs)

- PMR-1 A juvenile animal toxicology study of rimegepant in rat.
- PMR-2 Deferred pediatric open-label, single-dose study to evaluate the safety, tolerability, and single-dose PK of rimegepant in patients with migraine age 6 to <12 years of age.
- PMR-3 Deferred pediatric randomized, double-blind, placebo-controlled efficacy and safety study under PREA for the treatment of acute migraine with or without aura in patients ages 6 through 17. This study includes an initial single-blind placebo lead-in to identify patients who respond to placebo. This efficacy study must be designed to show superiority of rimegepant over placebo and is to be submitted as a special protocol assessment (SPA).
- PMR-4 Deferred pediatric open-label safety study under PREA to evaluate the long-term safety of intermittent treatment in patients ages 6 through 17, for up to one year.
- PMR-5 A pre- and postnatal development study of rimegepant in rat.

- PMR-6 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 rimegepant during pregnancy with two unexposed control populations: one consisting of women with migraine who have not been exposed to rimegepant 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-7 A pregnancy outcomes study using a different study design than provided for in PMR-6 (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 rimegepant during pregnancy compared to an unexposed control population.
- PMR-8 A clinical pharmacokinetic trial to evaluate the effect of a known P-gp inhibitor and BCRP inhibitor on the pharmacokinetics of rimegepant to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions.”

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/s/

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