CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL REVIEW(S)

CLINICAL REVIEW

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Division/Office	Division of Neurology 2/Office of New Drugs
Reviewer Name(s)	Laura Jawidzik, MD
Review Completion Date	02/26/2020
Established/Proper Name	Rimegepant
(Proposed) Trade Name	(b) (4) Nurtec-ODT
Applicant	Biohaven
Dosage Form(s)	Tablet, and oral disintegrating tablet (ODT)
Applicant Proposed Dosing Regimen(s)	75 mg orally
Applicant Proposed Indication(s)/Population(s)	Acute treatment of migraine with or without aura
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of acute migraine with or without aura

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Glossary

AC	advisory committee
ADaM	analysis data model
AE	adverse event
AHS	American Headache Society
AAN	American Academy of Neurology
AR	adverse reaction
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CK	creatine kinase
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CV	cardiovascular
DBP	diastolic blood pressure
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
EOP2	end-of-phase 2
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent-to-treat
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities

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mITT	modified intent-to-treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
ODT	oral disintegrating tablet
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	preferred term
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SDTM	study data tabulation model
SGE	special government employee
SOC	standard of care
SPF	sustained pain freedom
SPR	sustained pain relief
TEAE	treatment emergent adverse event

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1. Executive Summary

1.1. Product Introduction

Rimegepant (previously BMS-927711 and BHV-3000) is a small molecule, orally administered, calcitonin gene-related peptide (CGRP) receptor antagonist. CGRP is a potent vasodilator in the cerebral, coronary, and renal vascular beds (Russell et al. 2014). CGRP has been shown to have a role in migraine pathophysiology. Plasma CGRP levels increase during migraine attacks and infusion of CGRP has been shown to induce migraine-like attacks in susceptible people (Hansen et al. 2010). Rimegepant competes with the binding of CGRP and inhibits the function of CGRP at its receptor.

The applicant has proposed a dose of 75 mg orally with a maximum daily dose of 75 mg. A single dose (i.e., 75 mg) was evaluated in pivotal clinical efficacy studies. Rimegepant is intended to be prescribed for the acute treatment of migraine with or without aura.

Rimegepant is a new molecular entity (NME). There is one FDA-approved orally administered, small molecule CGRP receptor antagonist for the acute treatment of migraine (i.e., ubrogepant). There are three FDA-approved monoclonal antibodies (i.e., erenumab, fremanezumab, and galcanezumab) that act on the CGRP pathway and are indicated for the preventive treatment of migraine.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant has provided substantial evidence of effectiveness to support approval. The applicant provided data from three adequate and well-controlled studies that demonstrated that rimegepant is effective for the acute treatment of migraine as compared to placebo. Two of these studies utilized a tablet form of rimegepant and the third study utilized an oral disintegrating tablet (ODT). The applicant established effectiveness utilizing the co-primary endpoints that the Division considers clinically meaningful. The applicant has demonstrated statistical significance for the 75 mg dose on the co-primary endpoints: pain freedom and absence of most bothersome symptom at two hours after dosing. In addition, the applicant has demonstrated clinical and statistical significance on several key secondary endpoints. I recommend approval of rimegepant 75 mg for the acute treatment of migraine in adults.

1.3. Benefit-Risk Assessment

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Benefit-Risk Integrated Assessment

Rimegepant is a small molecule, orally administered, calcitonin gene-related peptide (CGRP) receptor antagonist. It is intended to be prescribed for the acute treatment of migraine with or without aura. Rimegepant was evaluated in clinical trial in two formulations: a tablet and an orally disintegrating tablet (ODT).

Migraine is a very common, chronic neurological condition with a broad spectrum of frequency and severity. It is characterized by recurrent attacks of headache with accompanying symptoms of nausea, vomiting, photophobia, and phonophobia. These attacks are of moderate to severe intensity and can at times be disabling and impact the quality of patients' lives. There are many FDA-approved drugs for the acute treatment of migraine. The drugs used to treat acute migraine include triptans, ergotamines, nonsteroidal anti-inflammatory medications (NSAIDs), a CGRP receptor antagonist, as well as combination products. They all have limitations, especially related to safety and tolerability.

The efficacy of rimegepant was demonstrated in three nearly identically designed randomized clinical studies. Two of the studies evaluated the tablet formulation and one study evaluated the use of an ODT. All three studies evaluated the effect of rimegepant on a single migraine attack. The co-primary endpoints used by the applicant are described in the Migraine Guidance for Industry and are accepted by the Division as clinically meaningful endpoints. The applicant has demonstrated statistical significance for the 75 mg dose on the co-primary endpoints: pain freedom and absence of most bothersome migraine symptom (i.e., phonophobia, photophobia, or nausea) at two hours after dosing. Compared with placebo-treated patients, 5-10% more rimegepant-treated patients were pain free and 8-12% more were free from their most bothersome symptom at 2 hours after dosing.

The safety profile of rimegepant was characterized in three pivotal single-dose studies and a long-term open-label study with repeat dosing. No major, serious toxicities were identified in these trials. Common adverse events in the double-blind portion of clinical trials that occurred in ≥1% of rimegepant-treated patients included various infections, dyspepsia, and nausea. Common adverse events occurring in the open-label study in ≥2% of rimegepant-treated patients included dyspepsia, nausea, abdominal pain, arthralgias, somnolence, dizziness, diarrhea, and headache. Clinical studies included generally younger, healthy patients and effectively excluded patients with major cardiovascular disease.

I recommend a postmarketing requirement (PMR) for a pregnancy registry and outcome study along with the required Pediatric Research Equity Act (PREA) PMRs for the study of pediatric migraine. These PMRs combined with enhanced pharmacovigilance for stroke and

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myocardial infarction, and product labeling will address the risks associated with rimegepant in the postmarketing setting.

I recommend approval of rimegepant 75 mg for the acute treatment of migraine with or without aura in adults. The efficacy of the product is similar to other approved products for the acute treatment of migraine and the tolerability appears to be an improvement over other approved products for the acute treatment of migraine.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Migraine is a very common, chronic neurological disease with a broad spectrum of frequency, and severity. It is characterized by recurrent attacks of headache that are typically moderate to severe in intensity. The attacks tend to be unilateral headaches associated with other symptoms such as nausea, vomiting, phonophobia, or photophobia. A typical migraine can be exacerbated by even minor physical activity and may last anywhere from 4 hours to 72 hours. Some patients may experience an aura 30 minutes to an hour prior to the onset of their headache, and other patients may experience a general prodrome a day or two prior to the onset of the headache. Migraine is more frequent in females than in males. In a large U.S. population-based study, the one-year prevalence of migraine was 18% in females and 7% in males and 12% overall (Lipton et al. 2001). Migraine prevalence peaks in the 4th decade of life for both males and females (Lipton et al. 2007).	Migraine can be a serious and at times disabling condition that can impact the quality of patients' lives.
Current Treatment Options	There are many FDA-approved therapies for the treatment of acute migraine, as well as many others that are used off-label. FDA-approved therapies include ergotamines, triptans, NSAIDs (both OTC and prescription), a CGRP receptor antagonist, devices, and combination products. Triptans are contraindicated in patients with a history of coronary artery disease, peripheral vascular disease, ischemic bowel disease, uncontrolled	Additional treatments for the acute treatment of migraine would be desirable, especially for patients with contraindications to currently available treatments or for patients who do not respond to currently available treatment.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	hypertension, transient ischemic attack, and stroke. Ergotamines are contraindicated in patients with cardiovascular disease. NSAIDs have an increased risk of serious gastrointestinal and cardiovascular adverse events.	
Benefit	The applicant conducted three pivotal efficacy studies that demonstrate the efficacy of rimegepant for the acute treatment of migraine. For all three studies, the applicant utilized the co-primary endpoints of migraine pain freedom and the absence of the most bothersome symptoms at 2 hours after dosing. Compared with placebo-treated patients, 5-10% more rimegepant-treated patients were pain free at 2 hours and 8-12% more were free from their most bothersome symptom at 2 hours. The efficacy of rimegepant is also supported by the results of several key secondary endpoints. In study 303, rimegepant 75 mg demonstrated statistical significance for the following secondary endpoints: pain relief at 2 hours after dosing, sustained pain freedom at 24 hours, reduction in the use of rescue medication, and improvement in functional disability at 2 hours after dosing. Compared to placebo-treated patients, 10-16% of rimegepant-treated patients experienced pain relief at 2 hours, and 5-10% experienced sustained pain freedom at 24 hours. In terms of rescue medication, 11-16% fewer rimegepant-treated patients required the use of rescue medication compared to placebo-treated patients. Nine to 16% of rimegepant-treated patients experienced no functional disability at 2 hours after dosing as compared to placebo-treated patients. Subgroup analyses suggest absent to reduced efficacy in patients ≥ age 65, and male patients.	The efficacy of rimegepant for the acute treatment of a migraine attack in patients with migraine with and without aura has been established. Rimegepant-treated patients are more likely than placebo-treated patients to be migraine pain free and free of their most bothersome migraine symptom at 2 hours after dosing. I recommend approval of the 75 mg dose of rimegepant.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	No serious safety issues related to the use of rimegepant were identified during this review. Several theoretical safety issues related to the use of CGRP receptor antagonists were reviewed in detail: cardiovascular, cerebrovascular, peripheral vascular, gastrointestinal, and liver toxicity. No clear safety signals were detected upon review of these issues. Common adverse events in the double-blind portion of clinical trials that occurred in ≥1% of rimegepant-treated patients included various infections, dyspepsia, and nausea. Common adverse events occurring in the open-label study in ≥2% of rimegepant-treated patients included dyspepsia, nausea, abdominal pain, arthralgias, somnolence, dizziness, diarrhea, and headache. Clinical trials included generally younger, healthy patients and effectively excluded patients with major cardiovascular disease. A Medication Guide does not appear to be needed. A pregnancy registry and outcome study will be a postmarketing requirement.	Rimegepant has an acceptable safety profile for the migraine population. However, safety issues have not been adequately evaluated in the population of patients with major cardiovascular disease. Enhanced pharmacovigilance will be used to address potential safety issues associated with the theoretical cardiovascular risk associated with CGRP receptor antagonism.

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1.4. Patient Experience Data

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

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

2. Therapeutic Context

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2.1. Analysis of Condition

Migraine is a very common, chronic neurological disease with a broad spectrum of frequency and severity. Migraine can be a serious and at times disabling condition that can impact the quality of patients' lives.

Migraine is a disease characterized by recurrent attacks of headache that are typically moderate to severe in intensity. The attacks tend to be unilateral headaches associated with symptoms such as nausea, vomiting, phonophobia, or photophobia. A typical migraine can be exacerbated by even minor physical activity and may last from 4 to 72 hours. Some patients may experience an aura 30 minutes to an hour prior to the onset of their headache, and other patients may experience a general prodrome a day or two prior to the onset of the headache.

Migraine is more frequent in females than in males. In a large U.S. population-based study, the one-year prevalence of migraine was 18% in females, 7% in males, and 12% overall (Lipton et al. 2001). Migraine prevalence peaks in the 4th decade of life for both males and females (Lipton et al. 2007). Although the prevalence of migraine declines with age, prevalence estimates in the population age 60+ is about 5% for females, and 1.6% for males (Lipton et al. 2007). Another estimate by Bigal and Lipton (2006) shows that the prevalence of migraine in the age 70+ population is about 4% with a 2% prevalence for males, and 5% prevalence for females.

2.2. Analysis of Current Treatment Options

There are many FDA-approved therapies including drugs and devices for the treatment of acute migraine, as well as many other drugs that are used off-label. The American Headache Society (AHS) published an assessment of the evidence for the acute treatment of migraine in 2015 (Marmura et al. 2015).

The evidence assessment classifies the following drugs as having Level A evidence (established as effective): acetaminophen, dihydroergotamine (DHE), aspirin, diclofenac, ibuprofen, naproxen, butorphanol nasal spray, triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, and combination acetaminophen/aspirin/caffeine, sumatriptan/naproxen.

The following drugs and combination products are considered by this assessment to have Level B evidence (probably effective): chlorpromazine, droperidol, metoclopramide, prochlorperazine, flurbiprofen, ketoprofen, ketorolac, IV magnesium, isometheptene, dihydroergotamine (SC, IV, IM); ergotamine/caffeine; tramadol/acetaminophen; and codeine/acetaminophen.

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The following drugs and combination products are considered by this assessment to have Level C evidence (possibly effective): valproate (IV), phenazone, codeine, ergotamine, butorphanol (IM), meperidine, methadone, tramadol, dexamethasone, lidocaine (intranasal); butalbital/acetaminophen/caffeine, and butalbital/acetaminophen/caffeine/codeine.

A subset of the above listed drugs is FDA-approved for the treatment of acute migraine (Table 1). Although there are numerous options for the acute treatment of migraine, the current FDA-approved treatments all have some limitations especially related to safety and tolerability of the treatment.

Table 1 Summary of FDA-Approved Treatments for Acute Migraine

Product Type	Product Name(s)	Year of Initial Approval	Administration	Important Safety and Tolerability Issues
Ergotamine	DHE	1946	Injection; nasal spray	Contraindicated in cardiovascular disease; fibrotic complications may occur with prolonged use
Triptans	Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan	1995	Tablets, nasal spray, SC injection, nasal powder	Contraindicated in patients with coronary artery disease, coronary artery vasospasm, conduction pathway disorders, cerebrovascular disease, hemiplegic/basilar migraine, peripheral vascular disease, ischemic bowel disease or uncontrolled hypertension; Warnings in patients with history of myocardial ischemia, arrhythmias, cerebral hemorrhage, subarachnoid hemorrhage or stroke
NSAIDs	Diclofenac, Ibuprofen (OTC)	2009	Oral dissolving packet, tablet	Cardiovascular risk for thrombotic events, myocardial infarction and stroke; gastrointestinal adverse events
Devices	GammaCore, Cerena, Cefaly	2013	Various	Contraindicated in patients with magnetic metals in head, neck or upper body, or pacemakers, or other implanted devices (Cerena); Contraindicated with recent trauma to skull/face or with skin conditions/rashes (Cefaly)
Combination products	Excedrin migraine, sumatriptan/ naproxen	2008	Tablets	Same as triptan/NSAID risks
5-HT1F receptor agonist	Lasmiditan	2019	Oral	Sedation; serotonin syndrome; abuse potential
CGRP receptor antagonists	Ubrogepant	2019	Oral	Somnolence; nausea

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3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

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

3.2. Summary of Presubmission/Submission Regulatory Activity

The investigational new drug (IND) application 109886 was opened on October 22, 2010, for rimegepant for the acute treatment of migraine. At that time, the sponsor of the IND was Bristol-Myers Squibb. The primary safety concern was the potential for hepatotoxicity because of a potential class effect seen with other small molecule CGRP receptor antagonists. The 'May Proceed' notification was issued November 18, 2010. A 'May Proceed' letter was issued April 1, 2011.

On September 1, 2011, the Division had an end-of-phase 1 (EOP1) meeting with the applicant. At that time the applicant proposed to use [redacted] (b) (4) as the primary endpoint for the phase 3 trials. The Division disagreed with the use of a composite endpoint for the primary endpoint. At the time of EOP1, the applicant had become aware of hepatoxicity in the development program for telcagepant, another small molecule CGRP antagonist. Because of this, the applicant proposed to do a dedicated hepatic safety study for their product. The proposal at that time was to give double-blinded study drug daily to patients for three months. The Division was in agreement with that plan; however, this study was never conducted.

In August 2016, the sponsorship of the IND changed from Bristol-Myers Squibb to Biohaven Pharmaceutical Holding Company.

On March 1, 2017, the Division had a Type B end-of-phase 2 (EOP2) meeting with the applicant. At EOP2, the Division and the applicant discussed the design of the single-attack, phase 3 studies. The applicant agreed to the use of the co-primary endpoints of pain freedom and freedom from most bothersome symptom at 2 hours after dosing. The Division indicated that the applicant did not need to "spend alpha" on the individual migraine symptoms of photophobia, phonophobia, and nausea at 2 hours post dose. The applicant indicated that they would also be developing an oral disintegrating tablet as well as a regular tablet. The Division reminded the applicant that Bristol-Myers Squibb had committed to doing a 3-month safety study in order to evaluate whether there is hepatoxicity associated with rimegepant. The applicant indicated that the study was never conducted and that their current plan was to enrich the long-term safety study with more frequent users of rimegepant. The Division

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expressed concern that this would not be adequate and asked for at least 600 patients at 6 months and 300 patients at 12 months treating on average two migraines per month. In addition, the Division asked for an assessment of patients taking daily or nearly daily rimegepant.

In January 2018, the Division had a Type C WRO with the applicant regarding claims the applicant was intending to make in labeling. The applicant asked if including (b) (4) The applicant was directed to the "Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products" to help guide in designing a trial that would allow for a such a claim. The Division told the applicant that to get a labeling claim for (b) (4) The applicant asked about including an analysis of a subgroup of patients with (b) (4) in section 6 of the label. The Division felt that discussion of what may be included in product labeling was premature. At this meeting the applicant also alerted the Division to a problem with their eDiary. The applicant noted that there were software problems that could potentially impact the amount of missing data in the study. The applicant noted that the problems with the eDiary were corrected and that the sample size for each study would potentially be increased. The Division noted their concerns about the amount of missing data.

In March 2019, the pre-NDA meeting was held with the applicant. The Division and the applicant came to agreement on the proposed safety pools and analyses for the pools. The applicant advised the Division of their plan to submit an NDA for their tablet followed by an NDA for the ODT product. The Division strongly recommended that the applicant submit both NDAs concurrently. The Division asked for the applicant to provide a discussion of the missing data and the impact of the device software problems on the data.

Summary of dates for regulatory interactions:
Initial IND: October 22, 2010
End-of-phase 1 meeting: September 1, 2011
End-of-phase 2 meeting: March 1, 2017
Pre-NDA meeting: March 4, 2019
NDA submission: June 27, 2019

3.3. Foreign Regulatory Actions and Marketing History

Rimegepant is not approved or marketed in any foreign country.

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

4.1. Office of Scientific Investigations (OSI)

OSI conducted inspections of seven clinical sites and the study sponsor, Biohaven Pharmaceuticals in support of both NDAs (b) (4) and 212728. There were three sites inspected for study 301, two sites for study 302, and three sites for study 303.

The inspection of site 002 for study 303 found significant data integrity issues related to good clinical practice noncompliance. The inspection of the study sponsor identified issues with the electronic patient-reported outcome (ePRO) devices. Issues identified included design and validation issues, inadequate user acceptance testing, and insufficient training of patients and study personnel on the use of the ePRO devices.

In the other sites that were inspected, there was no evidence of under-reporting adverse events. The electronic diary source data for the primary efficacy endpoint and the subject paper diaries for tracking the use of concomitant rescue medications were reviewed and verified against the data listings provided by the applicant. No discrepancies were noted.

Reviewer's comment: The applicant notified the Division of both of these issues during development. The Division recommended that the applicant conduct a sensitivity analysis of study 303 that omitted the data from site 002. In regard to the ePRO devices, the applicant provided datasets with patient level flags to help the reviewers determine the impact of potential missing data from the ePRO device issues.

4.2. Product Quality

Please see the Integrated Quality Review.

4.3. Nonclinical Pharmacology/Toxicology

Please see the review by Dr. David Carbone, nonclinical reviewer.

4.4. Clinical Pharmacology

Please see the review by Dr. Girish Bende, clinical pharmacology reviewer. I have summarized some of the major findings from his review in this section.

Rimegepant is rapidly absorbed under fasting conditions with a Tmax 1.5 hours for the ODT and 1.9 hours for the tablet. The mean terminal elimination half-life is approximately 11 hours.

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Rimegepant exhibits linear pharmacokinetics following a single oral administration over the dose range of 25 to 150 mg. A greater than dose proportional increase was observed from 300 to 600 mg.

CYP3A4 is the primary enzyme involved in the metabolism of rimegepant with CYP2C9 playing a lesser role as well. Co-administration with a strong CYP3A4 inducer may cause a loss of efficacy. Strong CYP3A inhibitors cause an increase in rimegepant exposure.

Food effect evaluation for the 75 mg dose showed that administration of rimegepant with a high-fat meal delayed the time to maximum plasma concentrations by about 1 hour and reduced the Cmax by about 33-53% with 32-38% change in the AUC.

The applicant conducted study 18 in hepatically impaired patients with pre-existing mild (6), moderate (6), or severe (6) hepatic impairment. Per Dr. Bende, the exposure of rimegepant was found to be increase by 2 to 2.5-fold in patients with severe hepatic impairment compared to healthy controls. The applicant proposes (b) (4) The applicant conducted a pharmacokinetic study in renally impaired patients. Per Dr. Bende there were no clinically meaningful differences in the pharmacokinetics of rimegepant compared to subjects with normal renal function. Per Dr. Bende, no dose or dosing frequency adjustment is required in patients with renal impairment.

4.5. Devices and Companion Diagnostic Issues

N/A

4.6. Consumer Study Reviews

N/A

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

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Table 2 Clinical Trials Relevant to the Treatment of Acute Migraine

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration	No. of patients treated	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
Study 301	Randomized, double-blind, placebo-controlled (pivotal efficacy)	75 mg orally tablet	Pain freedom at 2 hours; freedom from MBS	Single attack	1084	Hx of episodic migraine; 18+	50/1
Study 302	Randomized, double-blind, placebo-controlled (pivotal efficacy)	75 mg orally tablet	Pain freedom at 2 hours; freedom from MBS	Single attack	1072	Hx of episodic migraine; 18+	50/1
Study 303	Randomized, double-blind, placebo-controlled (pivotal efficacy)	75 mg orally Oral disintegrating tablet (ODT)	Pain freedom at 2 hours; freedom from MBS	Single attack	1351	Hx of episodic migraine; 18+	70/1
Studies to Support Safety							
Study 201	Open-label extension; repeat dosing	75 mg orally as needed; 75 mg QOD and PRN	Safety/tolerability	Up to one year	1784	Hx of episodic migraine; 18+	105/1

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5.2. Review Strategy

The applicant has proposed the 75 mg dose as the to-be-marketed dose. There are three pivotal studies that assessed the 75 mg dose: two studies that utilized the tablet, and an additional study that utilized the ODT formulation. This review will evaluate the data for all three pivotal studies to determine whether the 75 mg dose is approvable based on the efficacy and safety profile of the 75 mg dose. For efficacy, studies 301, 302, and 303 will be reviewed. For safety, these three studies (301, 302, and 303) plus the results of the long-term open-label safety study (201) will be reviewed.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 301: A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Safety and Efficacy Trial BHV-3000 (Rimegepant) for the Acute Treatment of Migraine

6.1.1. Study Design

Overview and Objective

The primary objective of this study was to evaluate the effect of rimegepant compared to placebo for the acute treatment of a single migraine attack and to evaluate the safety and tolerability of rimegepant.

Trial Design

Study 301 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of patients with history of migraine with or without aura. The study was conducted in 50 centers in the United States. In this study, patients treated a single qualifying migraine with a single dose of rimegepant or placebo. Patients were randomized in a 1:1 ratio to receive either placebo or rimegepant 75 mg. Randomization was stratified by the use of the preventive medications for migraine (yes or no). After a patient was randomized into the study, the patient had 45 days to treat a qualifying migraine with investigational product (IP). Patients were discontinued from the study if they did not treat a qualifying migraine within this time frame. Patients were NOT given the option to take a second dose of IP. Patients who completed the double-blind treatment period had the option to continue into the open-label extension study.

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Basic Study Design

Screening Period: up to 28 days prior to randomization
Treatment period: up to 45 days to treat a single migraine attack
Follow-up: 7 days after treatment

Figure 1 Study 301: Study Flow Chart

This figure was taken from the protocol for study 301

Diagnostic Criteria

The applicant utilized the International Classification of Headache Disorders, 3rd edition, beta for the diagnosis of migraine.

Treatment of a Qualifying Migraine

Patients had 45 days to treat a qualifying migraine attack at home. Patients were instructed to treat a migraine when the following conditions were met:

-migraine attack reaches a moderate or severe intensity
-diary questions regarding current pain and symptoms were answered

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Key Inclusion Criteria

1. Male or female patients age ≥18 years and older
2. At least one-year history of migraine with or without aura
3. Migraine onset prior to age 50
4. Less than 15 days with headaches per month in each of the 3 months prior to screening

Key Exclusion Criteria

1. Hemiplegic or basilar migraine
2. History of HIV, hepatitis B or C
3. History of uncontrolled, unstable, or recently diagnosed cardiovascular disease including ischemic heart disease, coronary artery disease, cerebral ischemia. Patients with a history of myocardial infarction, acute coronary syndrome, percutaneous coronary intervention, cardiac surgery, stroke, or transient ischemic attack during the 6 months prior to screening
4. Diagnosis of major depression, pain syndromes, psychiatric conditions, dementia, or significant neurological disorders
5. History of gastric or small intestinal surgery or has a disease that causes malabsorption
6. History of alcohol or drug abuse
7. ECG findings including left or right bundle branch block; QT interval > 470 msec; QRS≥ 150 msec
8. Serum bilirubin >1 x ULN; neutrophil count ≤1000/uL; AST or ALT > 1xULN

Dose Selection

In a phase 2 study, the applicant evaluated rimegepant compared to placebo for the treatment of acute migraine. This study included a placebo arm, a sumatriptan 100 mg arm, and the following doses of rimegepant: 10, 25, 75, 150, 300, and 600 mg. This was a single attack study and the primary endpoint was migraine pain freedom at 2 hours after dosing. In this study three doses of rimegepant (75, 150, and 300 mg) were effective for the acute treatment of migraine. The applicant felt that there was little meaningful gain in efficacy in the doses higher than 75 mg.

Study Treatments/Blinding

This was a double-blind placebo-controlled trial. IP was administered in 75 mg tablets or matching placebo.

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Assignment to Treatment

An automated interactive web response system (IWRS) was used to manage randomization and treatment assignment. All patients who met study entry criteria were randomized and provided enough IP to treat one migraine attack. Patients were randomized in a 1:1 ratio to either placebo or 75 mg of rimegepant. Randomization was stratified by current use of preventive medications (yes/no).

Dose Modification/Dose Discontinuation

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

Procedures and Schedule

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

Table 3 Schedule of Procedures and Assessments for Study 301

	Screening	Randomization	Treatment	End of Treatment Visit
Vital signs, Sheehan Suicidality Tracking Scale	x	x		x
ECG, physical exam, labs	x			x
Pregnancy test	x	x	x	x
IP dispensed		x		
IP administered			x	

Dietary Restrictions/Instructions

N/A

Concurrent Medications

The following substances were prohibited prior to randomization and during the course of this study or as specified:

-St. John's wort, butterbur root or extracts, marijuana
-History of use of ergotamine medications on ≥ 10 days/month

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-History of non-narcotic analgesic intake on ≥ 15 days/month for ≥ 3 months
-Use of narcotic medication such as barbiturates, morphine, codeine, oxycodone, and hydrocodone
-Use of acetaminophen or acetaminophen-containing products at daily dosing levels

Patients were permitted to remain on preventive medications for migraines provided the dose had been stable for at least 3 months prior to study entry.

Treatment Compliance

Compliance was monitored by counting the number of tablets dispensed and returned.

Rescue Medication

Rescue medication could only be taken beginning two hours after the initial dose of IP was taken. Patients were NOT given a second dose of IP to take. Patients were allowed the following rescue medication two hours after dosing if needed: aspirin, ibuprofen, acetaminophen, Naprosyn, antiemetics, baclofen. After 48 hours of administering IP, patients were allowed to use their standard of care rescue medications for the acute treatment of migraine including triptans.

Subject Completion/Discontinuation/Withdrawal

Patients could voluntarily withdraw from the study at any time. The reason for discontinuation was to be documented on the eCRF. All randomized patients who discontinued prematurely were to be seen for a final assessment. If the patient discontinued from the study after IP was taken, the patient was expected to return for the follow-up safety visit.

Study Endpoints

Co-Primary Endpoints

1. Pain freedom two hours after the initial dose
2. Absence of most bothersome symptom (MBS) two hours after the initial dose

Secondary Endpoints

1. Sustained pain freedom (SPF) from 2 to 24 hours
2. Photophobia freedom at 2 hours
3. Phonophobia freedom at 2 hours
4. Pain relief at 2 hours
5. Nausea freedom at 2 hours

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6. Probability of requiring rescue medication within 24 hours
7. Sustained pain freedom from 2 to 48 hours
8. Sustained pain relief (SPR) from 2 to 24 hours
9. Sustained pain relief from 2 to 48 hours
10. Proportion of patients able to work or function normally at 2 hours
11. Pain relapse from 2 to 48 hours

Definition of Pain Freedom

Defined as the reduction in headache severity from moderate or severe pain at baseline to no pain at two hours after the initial dose.

Definition of Pain Relief

Defined as the reduction in headache severity from moderate or severe pain to mild or no headache at two hours after the initial dose.

Definition of Sustained Pain Freedom

Defined as pain freedom with no administration of rescue medication, and with no occurrence of a headache of any intensity

Definition of Sustained Pain Relief

Defined as pain relief with no administration of rescue medication, and with no occurrence of a headache of moderate or severe intensity

Definition of Freedom from Functional Disability

Defined as a rating of 'normal' on a four-point functional disability scale: normal, mildly impaired, severely impaired, requires bedrest

Statistical Analysis Plan

Analysis Populations

Table 4 Study 301: Analysis Sets

Analysis Set	Definition
Intent-to-treat (ITT)	All randomized patients
Modified intent-to-treat (mITT)	All randomized patients who received at least 1 dose of IP and provided at least one efficacy measurement.
Safety	All patients who received ≥1 dose of IP

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For the secondary endpoints of photophobia, phonophobia, and nausea freedom at 2 hours, the mITT population included patients who reported that symptom at migraine onset.

Sample Size Estimation

The applicant used the results from the phase 2b study to calculate the sample size for the phase 3 studies. In the final SAP, the applicant estimated that 550 patients per treatment arm would provide 95% power to detect a difference on each of the co-primary endpoints. The initial sample size estimates from the protocol estimate 380 patients per treatment arm would provide 95% power to detect a difference on each of the co-primary endpoints.

Hypothesis Testing

Type I error was controlled in this study by using a hierarchical gate-keeping procedure. First, the two co-primary endpoints were tested. If the co-primary endpoints were found to be significant, then secondary endpoints were tested in a fixed sequence. Each co-primary endpoint was tested for superiority to placebo at a 2-sided alpha level of 0.05 without further adjustment for multiplicity. If the primary endpoint tests were both significant, then the secondary endpoints were tested in a fixed sequence, in the order shown above. If a test in the hierarchy was not significant, then it, and any further tests on endpoints in the sequence, would have p-values presented only for descriptive purposes, and no conclusions were to be drawn from those results.

Pre-Specified Methods for Handling Missing Data

A patient with missing data for the primary endpoint will be considered a treatment failure. Patients who take rescue medication before, or at, the time of the event of interest are classified as failures as well.

Protocol Amendments

Three protocol amendments were made to the original protocol which was released on April 12, 2017. Protocol version 2 was released July 11, 2017. This version allowed for the use of triptan as rescue medication provided that there were used 48 hours after the dose of IP was taken. The protocol added a specification that randomization will be stratified by the use of preventive medications for migraine (yes/no). The analysis of the primary endpoint was updated so that the last observation carried forward (LOCF) method would not be used. Protocol version 3 was released October 6, 2017. This protocol called for an increase in sample size. Protocol version 4 was released on January 23, 2018. The hierarchy for the testing of the secondary endpoints was changed. The analysis of the MBS was no longer stratified by MBS,

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only by use of preventive medication.

The first patient enrolled July 18, 2017, and last patient completed the study on January 26, 2018. Database lock was March 1, 2018.

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant asserts that the study was conducted in compliance with ICH E6 guidelines for good clinical practice (GCP). The applicant asserts that investigators obtained institutional review board (IRB) approval prior to study initiation.

Financial Disclosure

Please see Appendix 13.2.

Patient Disposition

Screened: 1485
Randomized: 1162 (placebo: 75 mg 580: 582)
Received at least 1 dose of double-blind IP: 1095 (placebo: 75 mg 549: 546)
mITT population: 1084 (placebo: 75 mg 541: 543)

The majority of randomized patients were included in the mITT (93%). In total there were 78 patients who were randomized, but not included in the mITT. There were 67 patients who were randomized, but not treated. There were only 11 patients who took IP but were not included in the mITT.

Table 5 Study 301: Randomized Patients Excluded from the mITT Population

Reason for Exclusion	Number of Patients
No post-baseline efficacy data	9
No moderate/severe migraine at baseline and no-post baseline data	1
No moderate or severe migraine at baseline	1

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Table adapted from IR response dated October 17, 2019, eCTD seq 0016, SD 17

Protocol Violations/Deviations

The most common protocol deviation was use of a prohibited concomitant medication. Overall the protocol deviations were low, generally balanced among treatment arms, and not expected to affect the primary efficacy outcome.

Table 6 Study 301: Protocol Deviations/Violations in the ITT Population

Protocol Deviation	Placebo N=580 n(%)	75 mg N=582 n(%)
Prohibited concomitant medication	30 (5.2)	24 (4.1)
Informed consent	10 (1.7)	14 (2.4)
Exclusion criteria	11 (1.9)	3 (0.5)

This table was adapted from the IR response dated December 2, 2019, eCTD seq no 0023.

Table of Demographic Characteristics

No baseline imbalance in the demographics were noted between placebo and treatment groups in the demographic characteristics (Table 7) or baseline migraine characteristics (

Table 8).

Table 7 Study 301: Demographic Characteristics of the mITT Population

Demographic Parameters	Placebo (N=541) n (%)	75 mg (N=543) n(%)
Sex		
Male	78 (14.4)	79 (14.5)
Female	463 (85.6)	464 (85.5)
Age		
Mean years (SD)	41.3 (12.1)	41.9 (12.3)
Median (years)	41.3	41.5
Min, max (years)	10.6, 71.0	18.6, 73.3
Age Group*		
18 to 40	264 (48.8)	265 (48.8)
41 to 64	261 (48.2)	264 (48.6)
65+	16 (3.0)	14 (2.6)
Race		
White	444 (82.1)	417 (76.8)

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Black or African American	80 (14.8)	107 (19.7)
Asian	7 (1.3)	6 (1.1)
American Indian or Alaska Native	3 (0.6)	1 (0.2)
Native Hawaiian/ Pacific Islander	0	2 (0.4)
Other/Multiple	7 (1.3)	10 (1.8)
Ethnicity		
Hispanic or Latino	68 (12.6)	58 (10.7)
Not Hispanic or Latino	473 (87.4)	485 (89.3)
Concomitant preventive medication		
Yes	94 (17.1)	84 (15.4)
Body Mass Index (BMI) kg/m²		
Mean (SD)	29.8 (7.7)	20.1 (7.7)
Median	28.3	29.2
Min, Max	15.8, 71	12.4, 61

This table was adapted from the CSR for study 301, table 10.2 and 14.5.3.3
*Age group was calculated by the reviewer in JMP using ADSL for study 301, analysis by planned treatment

Table 8 Study 301: Baseline Migraine Characteristics for the mITT Population

	Placebo N=541 n(%)	75 mg N=543 n(%)
Migraine headache severity*		
Moderate	377 (69.7)	396 (72.9)
Severe	164 (30.3)	147 (27.1)
Most bothersome symptom (MBS)**		
Photophobia	277 (51.2)	311 (57.3)
Phonophobia	77 (14.2)	65 (12.0)
Nausea	165 (30.5)	156 (28.7)
Missing	21 (3.9)	10 (1.8)

*Calculated by the reviewer from ADPAIN where ATPT=0 min, and ITTFL=Y, analysis by TRTP
**Adapted from the table 14.2.2 from the CSR for study 301.

Table 9 Study 301: Migraine History for the mITT Population

	Placebo N=541	75 mg N=543
Primary Migraine Type		
Without aura n(%)	358 (66.2)	353 (65.0)
With aura n(%)	183 (33.8)	190 (35.0)

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Average Frequency of Mod to Sev Migraines in the Last 3 months		
Median	4	4
Min, Max	2, 8	2, 11

Adapted from table 14.1.4.1 from the CSR for Study 301

There was one placebo-treated patient and one rimegepant-treated patient who reported their MBS after the IP was taken.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Rescue medication was taken more frequently by placebo-treated patients (36.4%) than by rimegepant-treated patients (24.5%). The most commonly used rescue medications were ibuprofen, acetylsalicylic acid/caffeine/acetaminophen, and acetaminophen. Triptans were not allowed for use as rescue until at least 48 hours had passed since taking IP.

Approximately 16% of patients were taking preventive medications for migraine. The most commonly used were topiramate, and amitriptyline.

Treatment compliance was not formally assessed. Patients were asked to return their study medication if they did not experience a migraine or did not take the IP within 45 days of the baseline visit.

Efficacy Results – Primary Endpoint

The co-primary endpoints for this study were as follows:

1. Pain freedom two hours after the initial dose
2. Absence of most bothersome symptom (MBS) two hours after the initial dose

The efficacy analyses were based on the mITT population. Statistically significant results were observed for the 75 mg dose compared to placebo for both co-primary efficacy endpoints (Table 10). These results were verified by the statistical reviewer, Dr. Jinnan Liu. She confirmed the applicant's analysis and calculation of the co-primary efficacy endpoints.

Table 10 Study 301: Results for the Co-Primary Efficacy Endpoints

	Placebo N= 541	75 mg N= 543
Pain Freedom at 2 hours		
Responders, n(%)	77 (14.2)	104 (19.2)
Difference from PBO		5%

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(95% CI)		(0.5, 9.3)
p-value		0.0298
NNT*		20
Absence of MBS at 2 hours		
Responders, n(%)	150 (27.7)	199 (36.6)
Difference from PBO		8.9%
(95% CI)		(3.4, 14.4)
p-value		0.0016
NNT*		11.1

This table was adapted from the CSR for study 301
*Number-needed-to-treat (NNT) was calculated by the reviewer

Data Quality and Integrity

There were no major data quality issues identified during the review of study 301. The data quality and analysis quality were adequate. The statistical reviewer was able to perform an independent review using the applicant's submitted datasets and confirmed the results of the applicant's analyses. There were some minor issues with data quality that are discussed in more detail in the statistical review by Dr. Jinnan Liu.

Efficacy Results – Secondary and other relevant endpoints

The following were the secondary efficacy endpoints which were tested hierarchically:

1. Photophobia freedom at 2 hours
2. Phonophobia freedom at 2 hours
3. Pain relief (PR) at 2 hours
4. Nausea freedom at 2 hours
5. Probability of requiring rescue medication within 24 hours
6. Sustained pain freedom (SPF) from 2 to 24 hours
7. Sustained pain relief (SPR) from 2 to 24 hours
8. Sustained pain freedom (SPF) from 2 to 48 hours
9. Sustained pain relief from 2 to 48 hours
10. Pain relapse from 2 to 48 hours
11. Proportion of patients able to work or function normally at 2 hours

Rimegepant 75 mg demonstrated statistically significant findings on 3 out of the 11 secondary endpoints, and nominal significance on 5 additional secondary endpoints (Table 11). Freedom from nausea at 2 hours was not statistically significant. Because of the hierarchical testing procedure, p-values for endpoints tested after freedom from nausea at 2 hours were descriptive only. All secondary endpoints tested after nausea freedom, except pain relapse from 2 to 48 hours were nominally significant.

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Table 11 Study 301: Secondary Endpoints Reaching Statistical Significance

	75 mg
Photophobia freedom	x
Phonophobia freedom	x
PR at 2 hours	x
Nausea freedom	
Rescue medication in 24 hours	y
SPF 2 to 24 hours	y
SPR 2 to 24 hours	y
SPF 2 to 48 hours	y
SPR 2 to 48 hours	y
Pain relapse from 2 to 48 hours	
Ability to work/function normally	y

x=statistical significance
y=nominal significance

Table 12 Study 301: Results for the Secondary Endpoints

	Placebo N=541	75 mg N=543
Absence of photophobia		
Responders, n/N (%)	120/483 (24.8)	164/470 (34.9)
Difference from PBO		10.1%
(95% CI)		(4.4, 15.9)
p-value		0.001
NNT*		9.9
Absence of phonophobia		
Responders, n(%)	133/345 (30.9)	113/366 (38.6)
Difference from PBO		7.7
(95% CI)		(0.8, 14.6)
p-value		0.030
NNT*		13.0
Pain relief at 2 hours		
Responders, n(%)	247/541 (45.7)	304/543 (56.0)
Difference from PBO		10.3
(95% CI)		(4.4, 16.2)

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	Placebo N=541	75 mg N=543
p-value		0.001
NNT*		9.7
Absence of nausea		
Responders, n(%)	134/322 (41.6)	149/318 (46.9)
Difference from PBO		5.2
(95% CI)		(-2.4, 12.9)
p-value		0.182
NNT*		19.2
Rescue medication in 24hrs		
Responders, n(%)	172 (31.8)	111 (20.4)
Difference from PBO		-11.3
(95% CI)		(-16.5, -6.2)
p-value**		0.0001
NNT*		8.8
SPF from 2 to 24 hrs		
Responders, n(%)	44 (8.1)	76 (14.0)
Difference from PBO		5.9
(95% CI)		(2.1, 9.6)
p-value**		0.002
NNT*		16.9
SPR from 2 to 24 hours		
Responders, n(%)	151 (27.9)	211 (38.9)
Difference from PBO		11.0
(95% CI)		(5.4, 16.5)
p-value**		<0.0001
NNT*		9.1
SPF from 2 to 48 hrs		
Responders, n(%)	39 (7.2)	63 (11.6)
Difference from PBO		4.4
(95% CI)		(0.9, 7.8)
p-value**		0.013
NNT*		22.7
SPR from 2 to 48 hrs		
Responders, n(%)	129 (23.9)	183 (33.7)
Difference from PBO		9.8
(95% CI)		(4.5, 15.2)
p-value**		<0.001
NNT*		10.2

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	Placebo N=541	75 mg N=543
Pain relapse from 2 to 48 hrs		
Responders, n(%)	38/77 (50.0)	41/104 (40.1)
Difference from PBO		-9.9
(95% CI)		(-24.4, 4.6)
p-value		0.180
NNT*		10.1
Freedom from functional disability		
Responders, n(%)	118 (21.8)	181 (33.3)
Difference from PBO		11.5
(95% CI)		(6.2, 16.8)
p-value**		<0.001
NNT*		8.7

This table was adapted from Table 11-2 in the CSR for study 301
*NNT was calculated by the reviewer
**Nominal p-value

Dose/Dose Response

N/A

Sensitivity Analyses Conducted on Study 301

The applicant conducted several sensitivity analyses on the primary endpoint. Two of these analyses relate to the timing of a software fix that was applied to the eDiary (Table 13). During the development of rimegepant, the applicant identified software problems with their eDiary and had their eDiary vendor apply a software fix to minimize further data loss. The applicant performed a sensitivity analysis on the data acquired prior to the software fix and after the software fix.

Table 13 Study 301: Sensitivity Analysis for Primary Endpoint Pain Freedom at 2 Hours

	Placebo N= 541	75 mg N= 543
Prior to Software Fix		
Pain Freedom at 2 hours		
Responders, n(%)	25/166 (15%)	29/172 (16.8%)
Difference from PBO		1.8%
(95% CI)	9.6, 20.5	11.3, 22.4
p-value		0.6495

Reference ID: 4566903

After Software Fix		
Pain Freedom at 2 hours		
Responders, n(%)	52/375 (13.9%)	75/371 (20.2%)
Difference from PBO		6.3
(95% CI)	10.4, 17.4	16.1, 24.3
p-value		0.0217

Missing data at two hours are imputed as failures. Patients who used rescue medication at or prior to 2 hours are imputed as failures. This table is adapted from the CSR for study 301, table 14.2.1.3.1

The applicant conducted a sensitivity analysis on the primary endpoint using applying the last observation carried forward (LOCF) method (Table 14).

Table 14 Study 301: Sensitivity Analysis using LOCF

	Placebo N= 541	75 mg N= 543
Pain Freedom at 2 hours		
Responders, n(%)	79 (14.6%)	107 (19.7%)
Difference from PBO		5.1%
(95% CI)	11.6, 17.6	16.4, 23.1
p-value		0.0258

This table was adapted from the CSR for study 301, table 14.2.1.3.2

The applicant also conducted a sensitivity analysis called the 'complete case' analysis (Table 15). This analysis includes only those patients with data present at baseline and at 2 hours. This analysis is essentially an observed data only analysis.

Table 15 Study 301: 'Complete Case' Sensitivity Analysis

	Placebo N= 541	75 mg N= 543
Pain Freedom at 2 hours		
Responders, n(%)	77/514 (15%)	104/521 (20%)
Difference from PBO		5%
(95% CI)	11.9, 18.1	16.5, 23.4
p-value		0.0345

This table is adapted from the CSR for study 301, table 14.2.1.3.3

Reviewer's comment: The applicant-conducted sensitivity analyses support the primary endpoint analysis with the exception of the sensitivity analysis conducted on the data obtained prior to the software fix. Numerically the analysis is in favor of rimegepant, but the p-value is not significant. I suspect this result is because the sample size prior to the software fix is not

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large enough to detect a difference between placebo and active treatment.

6.2. Study 302: A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Safety and Efficacy Trial BHV-3000 (Rimegepant) for the Acute Treatment of Migraine

6.2.1. Study Design

Study 302 was identically designed to study 301. Please refer to section 6.1.1 Study Design for Study 301 as these elements are all applicable to study 302.

6.2.2. Study Results

Compliance with Good Clinical Practices

The applicant asserts that the study was conducted in compliance with ICH E6 guidelines for good clinical practice (GCP). The applicant asserts that investigators obtained institutional review board (IRB) approval prior to study initiation.

Financial Disclosure

Please see Appendix 13.2.

Patient Disposition

Screened: 1499
Randomized: 1186 (placebo: 75 mg 592:594)
Received at least 1 dose of double-blind IP: 1086 (placebo: 75 mg 543:543)
mITT population: 1072 (placebo: 75 mg 535:537)

The majority of randomized patients were included in the mITT (90.4%). In total there were 114 patients who were randomized, but not included in the mITT. There were 100 patients who were randomized, but not treated. There were only 14 patients who took IP but were not included in the mITT.

Table 16 Study 302: Randomized Patients Excluded from the mITT

Reason for Exclusion	Number of Patients
Randomized more than once	7 (see note below)

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No post-baseline efficacy data	6
No moderate or severe migraine at baseline and no post-baseline efficacy data	1

Table adapted from IR response dated October 17, 2019, eCTD seq 0016, SD 17

Note: There were 4 patients who were randomized twice. There were 8 subject IDs representing 4 unique patients. Three patients were randomized and treated with placebo twice. One patient was randomized to rimegepant twice, but only received treatment once. All four patients were excluded from the mITT. This accounts for seven 'patients' who received treatment but were excluded from the mITT.

Protocol Violations/Deviations

Overall the protocol deviations were low, generally balanced among treatment arms, and not expected to affect the primary efficacy outcome.

Table 17 Study 302: Protocol Deviations/Violations in the ITT Population

Protocol Deviation	Placebo N=592 n(%)	75 mg N=594 n(%)
Prohibited concomitant medication	25 (4.2)	20 (3.4)
Informed consent	24 (4.1)	30 (5.1)
Exclusion criteria	11 (1.9)	5 (0.8)

This table was adapted from the IR response dated December 2, 2019, eCTD seq no 0023.

Table of Demographic Characteristics

No baseline imbalance in the demographics were noted between placebo and treatment groups in the demographic characteristics (Table 18) or baseline migraine characteristics (Table 19).

Table 18 Study 302: Demographic Characteristics of the mITT Population

Demographic Parameters	Placebo (N=535) n (%)	75 mg (N=537) n(%)
Sex		
Male	58 (10.8)	63 (11.8)

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Female	479 (89.2)	472 (88.2)
Age		
Mean years (SD)	40.9 (12.1)	40.2 (11.9)
Median (years)	40.4	39.1
Min, max (years)	18.4, 83.6	18.1, 71.9
Age Group*		
18 to 40	277 (51.8)	298 (55.5)
41 to 64	241 (45.0)	230 (42.8)
65 +	17 (3.2)	9 (1.7)
Race		
White	399 (74.6)	394 (73.4)
Black or African American	118 (22.1)	111 (20.7)
Asian	8 (1.5)	8 (1.5)
American Indian or Alaska Native	5 (0.9)	4 (0.7)
Native Hawaiian or Other Pacific Islander	0	6 (1.1)
Other/Multiple	5 (0.9)	14 (2.6)
Ethnicity		
Hispanic or Latino	77 (14.3)	83 (15.5)
Not Hispanic or Latino	452 (84.5)	460 (85.7)
Concomitant preventive medication		
Yes	79 (14.5)	90 (16.6)
Body Mass Index (BMI) kg/m²		
Mean (SD)	31.8 (8.5)	31.0 (7.9)
Median	30.9	29.6
Min, Max	17.5, 75.7	14.8, 68.1

This table was adapted from the CSR for study 302, table 10.2 and 14.5.3.3
*Age group was calculated by the reviewer in JMP using ADSL for study 302, analysis by planned treatment

Table 19 Study 302: Baseline Migraine Characteristics for the mITT Population

	Placebo N= 535 n(%)	75 mg N=537 n(%)
Migraine headache severity*		
Moderate	349 (65.2)	354 (65.9)
Severe	186 (34.8)	183 (34.1)
Most bothersome symptom (MBS)**		
Photophobia	279 (52.1)	277 (51.6)
Phonophobia	92 (17.2)	72 (13.4)
Nausea	148 (27.7)	169 (31.5)
Missing	15 (2.8)	15 (2.8)

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*Calculated by the reviewer from ADPAIN where ATPT=0 min, and ITTFL=Y, analysis by TRTP
**Adapted from the table 14.2.2 from the CSR for study 302.

Table 20 Study 302: Migraine History for the mITT Population

	Placebo N=535	75 mg N=537
Primary Migraine Type		
Without aura n(%)	366 (68.4)	355 (66.1)
With aura n(%)	169 (31.6)	182 (33.9)
Average Frequency of Mod to Sev Migraines in the Last 3 months		
Median	4	4
Min, Max	2, 8	2, 11

Adapted from table 14.1.4.1 from the CSR for study 302

There was one placebo-treated patient and 4 rimegepant-treated patients who reported their MBS after study drug was taken.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Rescue medication was taken more frequently by placebo-treated patients (42.2%) than by rimegepant-treated patients (26.3%). The most commonly used rescue medications were ibuprofen, acetylsalicylic acid/caffeine/acetaminophen, and acetaminophen. Triptans were not allowed for use as rescue until at least 48 hours had passed since taking IP.

Approximately 15% of patients were taking preventive medications for migraine. The most commonly used were topiramate, and amitriptyline.

Treatment compliance was not formally assessed. Patients were asked to return their study medication if they did not experience a migraine or did not take the IP within 45 days of the baseline visit.

Efficacy Results – Primary Endpoint

The co-primary endpoints for this study were as follows:

1. Pain freedom two hours after the initial dose
2. Absence of most bothersome symptom (MBS) two hours after the initial dose

The efficacy analyses were based on the mITT population. Statistically significant results were observed for the 75 mg dose compared to placebo for both co-primary efficacy endpoints

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(Table 21). These results were verified by the statistical reviewer, Dr. Jinnan Liu. She confirmed the applicant's analysis and calculation of the co-primary efficacy endpoints.

Table 21 Study 302: Results for the Co-Primary Efficacy Endpoints

	Placebo N=535	75 mg N=537
Pain Freedom at 2 hours		
Responders, n(%)	64 (12.0)	105 (19.6)
Difference from PBO		7.6
(95% CI)		(3.3, 11.9)
p-value		<0.001
NNT*		13.2
Absence of MBS at 2 hours		
Responders, n(%)	135 (25.2)	202 (37.6)
Difference from PBO		12.4
(95% CI)		(6.9, 17.9)
p-value		<0.001
NNT*		8.1

This table was adapted from table 11-1 from the CSR for study 302
*Number-needed-to-treat (NNT) was calculated by the reviewer

Data Quality and Integrity

There were no major data quality issues identified during the review of study 302. The data quality and analysis quality were adequate. The statistical reviewer was able to perform an independent review using the applicant's submitted datasets and confirm the results of the applicant's analyses. There were some minor issues with data quality that are discussed in more detail in the statistical review by Dr. Jinnan Liu.

Efficacy Results – Secondary and other relevant endpoints

The following were the secondary efficacy endpoints which were tested hierarchically:

1. Photophobia freedom at 2 hours
2. Phonophobia freedom at 2 hours
3. Pain relief (PR) at 2 hours
4. Nausea freedom at 2 hours
5. Probability of requiring rescue medication within 24 hours
6. Sustained pain freedom (SPF) from 2 to 24 hours
7. Sustained pain relief (SPR) from 2 to 24 hours

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8. Sustained pain freedom (SPF) from 2 to 48 hours
9. Sustained pain relief from 2 to 48 hours
10. Pain relapse from 2 to 48 hours
11. Proportion of patients able to work or function normally at 2 hours

Rimegepant 75 mg demonstrated statistically significant findings on 3 out of the 11 secondary endpoints, and nominal significance on 5 additional secondary endpoints (Table 22 and Table 23). Freedom from nausea at 2 hours was not statistically significant. Because of the hierarchical testing procedure, p-values for endpoints tested after freedom from nausea at 2 hours were descriptive only. All secondary endpoints tested after nausea freedom, except pain relapse from 2 to 48 hours were nominally significant.

Table 22 Study 302: Secondary Endpoints Reaching Statistical Significance

	75 mg
Photophobia freedom	x
Phonophobia freedom	x
PR at 2 hours	x
Nausea freedom	
Rescue medication in 24 hours	y
SPF 2 to 24 hours	y
SPR 2 to 24 hours	y
SPF 2 to 48 hours	y
SPR 2 to 48 hours	y
Pain relapse from 2 to 48 hours	
Ability to work/function normally	y

x=statistical significance
y=nominal significance

Table 23 Study 302: Results for the Secondary Endpoints

	Placebo N=535	75 mg N=537
Absence of photophobia		
Responders, n/N (%)	106/477 (22.3)	183/489 (37.4)
Difference from PBO		15.1
(95% CI)		(9.4, 20.8)
p-value		<0.001
NNT*		6.6
Absence of phonophobia		

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	Placebo N=535	75 mg N=537
Responders, n(%)	100/374 (26.8)	133/362 (36.7)
Difference from PBO		9.9
(95% CI)		(3.2, 16.6)
p-value		0.004
NNT*		10.1
Pain relief at 2 hours		
Responders, n(%)	229/535 (42.8)	312/537 (58.1)
Difference from PBO		15.3
(95% CI)		(9.4, 21.2)
p-value		<0.001
NNT*		6.5
Absence of nausea		
Responders, n(%)	145/336 (43.3)	171/355 (48.1)
Difference from PBO		4.8
(95% CI)		(-2.7, 12.2)
p-value		0.208
NNT*		20.8
Rescue medication in 24hrs		
Responders, n(%)	198 (37.0)	113 (21.0)
Difference from PBO		-16.0
(95% CI)		(-21.3, -10.6)
p-value**		<0.001
NNT*		6.3
SPF from 2 to 24 hrs		
Responders, n(%)	38 (7.1)	66 (12.3)
Difference from PBO		5.2
(95% CI)		(1.7, 8.7)
p-value**		0.004
NNT*		19.2
SPR from 2 to 24 hours		
Responders, n(%)	142 (26.5)	229 (42.6)
Difference from PBO		16.1
(95% CI)		(10.5, 21.7)
p-value**		<0.001
NNT*		6.2
SPF from 2 to 48 hrs		
Responders, n(%)	32 (6.0)	53 (9.9)
Difference from PBO		3.9

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	Placebo N=535	75 mg N=537
(95% CI)		(0.7, 7.1)
p-value**		0.018
NNT*		25.6
SPR from 2 to 48 hrs		
Responders, n(%)	121 (22.6)	195 (36.3)
Difference from PBO		13.7
(95% CI)		(8.3, 19.1)
p-value**		<0.001
NNT*		7.3
Pain relapse from 2 to 48 hrs		
Responders, n(%)	32/64 (50.0)	52/105 (49.6)
Difference from PBO		-0.4
(95% CI)		(-15.8, 15.1)
p-value**		0.965
NNT*		250
Freedom from functional disability		
Responders, n(%)	125 (23.4)	175 (32.6)
Difference from PBO		9.2
(95% CI)		(3.9, 14.6)
p-value**		0.001
NNT*		10.9

This table was adapted from Table 11-2 in the CSR for study 302
*NNT was calculated by the reviewer
**Nominal p-value

Dose/Dose Response

N/A

Sensitivity Analyses Conducted on Study 302

The applicant conducted several sensitivity analyses on the primary endpoint. Two of these analyses relate to the timing of a software fix that was applied to the eDiary. During the development of rimegepant, the applicant identified software problems with their eDiary and had their eDiary vendor apply a software fix to minimize further data loss. The applicant performed a sensitivity analysis on the data acquired prior to the software fix and after the software fix.

Reference ID: 4566903

Table 24 Study 302: Sensitivity Analysis for Primary Endpoint Pain Freedom at 2 Hours

	Placebo N= 535	75 mg N= 537
Prior to Software Fix		
Pain Freedom at 2 hours		
Responders, n(%)	12/121 (9.9%)	23/116 (19.8%)
Difference from PBO		9.9%
(95% CI)	4.6, 15.2	12.6, 27.1
p-value		0.0308
After Software Fix		
Pain Freedom at 2 hours		
Responders, n(%)	52/414 (12.6%)	82/421 (19.5%)
Difference from PBO		6.9%
(95% CI)	9.4, 15.8	15.7, 23.3
p-value		0.0061

Missing data at two hours are imputed as failures. Patients who used rescue medication at or prior to 2 hours are imputed as failures. This table is adapted from the CSR for study 302, table 14.2.1.3.1

The applicant conducted a sensitivity analysis on the primary endpoint using applying the last observation carried forward (LOCF) method (Table 25).

Table 25 Study 302: Sensitivity Analysis using LOCF

	Placebo N= 535	75 mg N= 537
Pain Freedom at 2 hours		
Responders, n(%)	66 (12.3%)	108 (20.1%)
Difference from PBO		7.8%
(95% CI)	9.6, 15.1	16.7, 23.5
p-value		0.0005

This is adapted from the CSR for study 302, table 14.2.1.3.2

The applicant also conducted a sensitivity analysis called the 'complete case' analysis. This analysis includes only those patients with data present at baseline and at 2 hours. This analysis is essentially an observed data only analysis.

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Table 26 Study 302: 'Complete Case' Sensitivity Analysis

	Placebo N= 535	75 mg N=537
Pain Freedom at 2 hours		
Responders, n(%)	64/516 (12.4%)	105/510 (20.6%)
Difference from PBO		8.2%
(95% CI)	9.6, 15.3	17.1, 24.1
p-value		0.0004

This table is adapted from the CSR for study 302, table 14.2.1.3.3

Reviewer's comment: The applicant-conducted sensitivity analyses support the results of the primary endpoint analysis for pain freedom at 2 hours.

6.3. Study 303: A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Safety and Efficacy Trial BHV-3000 (Rimegepant) Orally Disintegrating Tablet (ODT) for the Acute Treatment of Migraine

6.3.1. Study Design

Study 303 was identically designed to study 301. The primary difference in this study is that the applicant utilized an ODT formulation rather than a tablet formulation for the study. Additionally, the applicant added additional secondary endpoints and re-ordered the testing sequence of the secondary endpoints in study 303. Please refer to section 6.1.1 Study Design for Study 301 as all other elements are applicable to study 303.

Note: Per the CSR for study 303, the ODT was to be placed under the tongue until fully dissolved and then swallowed.

6.3.2. Study Results

Compliance with Good Clinical Practices

The applicant asserts that the study was conducted in compliance with ICH E6 guidelines for good clinical practice (GCP). The applicant asserts that investigators obtained institutional review board (IRB) approval prior to study initiation.

Reference ID: 4566903

Financial Disclosure

Please see Appendix 13.2.

Patient Disposition

Screened: 1811
Randomized: 1466 (placebo: 75 mg 734:732)
Received at least 1 dose of double-blind IP: 1375 (placebo: 75 mg 693:682)
mITT population: 1351 (placebo: 75 mg 682:669)

The majority of randomized patients were included in the mITT (92.2%). In total there were 115 patients who were randomized, but not included in the mITT. There were 91 patients who were randomized, but not treated. There were only 24 patients who took IP but were not included in the mITT.

Table 27 Study 303: Randomized Patients Excluded from the mITT Population

Reason for Exclusion	Number of Patients
No post-baseline efficacy data	21
No moderate/severe migraine at baseline	3

Table adapted from IR response dated October 17, 2019, eCTD seq 0016, SD 17

Protocol Violations/Deviations

The most common protocol violation was use of a prohibited concomitant medication. Overall the protocol deviations were low, generally balanced among treatment arms, and not expected to affect the primary efficacy outcome.

Table 28 Study 303: Protocol Deviations/Violations in the ITT Population

Protocol Deviation	Placebo N=734 n(%)	75 mg N=732 n(%)
Prohibited concomitant medication	26 (3.5)	35 (4.8)
Informed consent	10 (1.4)	8 (1.1)
Exclusion criteria	9 (1.2)	7 (1.0)

This table was adapted from the IR response dated December 2, 2019, eCTD seq no 0023.

Reference ID: 4566903

Table of Demographic Characteristics

No baseline imbalance in the demographics were noted between placebo and treatment groups in the demographic characteristics (Table 29) or baseline migraine characteristics (Table 30).

Table 29 Study 303: Demographic Characteristics of the mITT Population

Demographic Parameters	Placebo (N=682) n (%)	75 mg (N=669) n(%)
Sex		
Male	103 (15.1)	101 (15.1)
Female	579 (84.9)	568 (84.9)
Age		
Mean years (SD)	40.0 (11.9)	40.3 (12.1)
Median (years)	38.9	39.7
Min, max (years)	18.1, 71.8	18.1, 75.7
Age Group*		
18 to 40	385 (56.5)	352 (52.6)
41 to 64	280 (41.1)	305 (45.7)
65+	17 (2.6)	12 (1.9)
Race		
White	521 (76.4)	496 (74.1)
Black or African American	125 (18.3)	141 (21.1)
Asian	19 (2.8)	8 (1.2)
American Indian or Alaska Native	3 (0.4)	4 (0.6)
Native Hawaiian or Other Pacific Islander	5 (0.7)	11 (1.6)
Other/Multiple	9 (1.3)	7 (1.0)
Ethnicity		
Hispanic or Latino	135 (19.8)	116 (17.3)
Not Hispanic or Latino	547 (80.2)	553 (82.7)
Concomitant preventive medication		
Yes	101 (14.6)	95 (13.9)
Body Mass Index (BMI) kg/m²		
Mean (SD)	30.6 (8.0)	31.1 (8.2)
Median	29.3	29.9
Min, Max	15.1, 69.7	16.5, 63.8

This table was adapted from the CSR for study 303, table 10.2 and 14.5.3.3; *Age group was calculated by the reviewer in JMP using ADSL for study 303, analysis by planned treatment

Reference ID: 4566903

Table 30 Study 303: Baseline Migraine Characteristics for the mITT Population

	Placebo N=682 n(%)	75 mg N=669 n(%)
Migraine headache severity*		
Moderate	490 (71.8)	473 (70.7)
Severe	192 (28.2)	196 (29.3)
Most bothersome symptom (MBS)**		
Photophobia	374 (54.8)	359 (53.7)
Phonophobia	101 (14.8)	108 (16.1)
Nausea	195 (28.6)	189 (28.3)
Missing	11 (1.6)	13 (1.9)

*Calculated by the reviewer from ADPAIN where ATPT=0 min, and ITTFL=Y, analysis by TRTP
**Adapted from the table 14.2.1.2 from the CSR for study 303.

There was one placebo-treated patient who reported the MBS after taking IP.

Table 31 Study 303: Migraine History for the mITT Population

	Placebo N=682	75 mg N=669
Primary Migraine Type		
Without aura n(%)	462 (67.7)	480 (71.7)
With aura n(%)	220 (32.3)	189 (28.3)
Average Frequency of Mod to Sev Migraines in the Last 3 months		
Median	4	4
Min, Max	2, 8	2, 8

Adapted from table 14.1.4.1 from the CSR for Study 303

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Rescue medication was taken more frequently by placebo-treated patients (34.5%) than by rimegepant-treated patients (18.3%). Triptans were not allowed for use as rescue until at least 48 hours had passed since taking IP.

Approximately 14% of patients were taking preventive medications for migraine. The most commonly used were topiramate, and amitriptyline.

Reference ID: 4566903

Treatment compliance was not formally assessed. Patients were asked to return their study medication if they did not experience a migraine or did not take the IP within 45 days of the baseline visit.

Efficacy Results – Primary Endpoint

The co-primary endpoints for this study were as follows:

1. Pain freedom two hours after the initial dose
2. Absence of most bothersome symptom (MBS) two hours after the initial dose

The efficacy analyses were based on the mITT population. Statistically significant results were observed for the 75 mg dose compared to placebo for both co-primary efficacy endpoints (Table 32). These results were verified by the statistical reviewer, Dr. Jinnan Liu. She confirmed the applicant's analysis and calculation of the co-primary efficacy endpoints.

Table 32 Study 303: Results for the Co-Primary Efficacy Endpoints

	Placebo N=682	75 mg N=669
Pain Freedom at 2 hours		
Responders, n(%)	74 (10.9)	142 (21.2)
Difference from PBO		10.3
(95% CI)		(6.5, 14.2)
p-value		<0.001
NNT*		9.7
Absence of MBS at 2 hours		
Responders, n(%)	183 (26.8)	235 (35.1)
Difference from PBO		8.3
(95% CI)		(3.4, 13.2)
p-value		0.001
NNT*		12.0

This table was adapted from the CSR for study 303
*Number-needed-to-treat (NNT) was calculated by the reviewer

Data Quality and Integrity

There were no major data quality issues identified during the review of study 303. The data quality and analysis quality are adequate. The statistical reviewer was able to perform an independent review using the applicant's submitted datasets and confirm the results of the applicant's analyses.

Reference ID: 4566903

Efficacy Results – Secondary and other relevant endpoints

For study 303, the applicant re-ordered the testing of the secondary endpoints. Nausea was moved to lower on the testing hierarchy because of the non-significant results from studies 301 and 302 on the nausea endpoint. The following were the secondary efficacy endpoints which were tested hierarchically:

1. Pain relief at 2 hours*
2. Functional disability at 2 hours*
3. Sustained pain relief from 2 to 24 hours
4. Sustained freedom from MBS from 2 to 24 hours
5. Probability of requiring rescue medication within 24 hours*
6. Sustained normal functioning from 2 to 24 hours
7. Sustained pain relief (SPR) from 2 to 48 hours
8. Sustained freedom from MBS from 2 to 48 hours
9. Sustained normal functioning from 2 to 48 hours
10. Photophobia freedom at 2 hours*
11. Functional disability at 90 minutes
12. Pain relief at 90 minutes
13. Sustained pain freedom (SPF) from 2 to 24 hours*
14. MBS freedom at 90 minutes
15. Pain freedom at 90 minutes
16. Phonophobia freedom at 2 hours*
17. Sustained pain freedom (SPF) from 2 to 48 hours*
18. Pain relief at 60 minutes
19. Functional disability at 60 minutes
20. Nausea freedom at 2 hours*
21. Pain relapse from 2 to 48 hours

All of the secondary endpoints reached statistical significance except for the last two: freedom from nausea at 2 hours, and pain relapse from 2 to 48 hours. The following table includes the results of the secondary endpoints that I think are most appropriate for inclusion in product labeling (Table 33). The analyses of the following secondary endpoints for study 303 were verified by the statistical reviewer: pain relief at 2 hours, sustained pain freedom at 24 and 48 hours, use of rescue medication within 24 hours, and freedom from functional disability at 2 hours.

Reference ID: 4566903

Table 33 Study 303: Results for the Secondary Endpoints

	Placebo N=682	75 mg N=669
Pain relief at 2 hours		
Responders, n/N (%)	295 (43.3)	397 (59.3)
Difference from PBO		16.0
(95% CI)		(10.8, 21.3)
p-value		<0.001
NNT*		6.3
Freedom from functional disability		
Responders, n(%)	176 (25.8)	255 (38.1)
Difference from PBO		12.3
(95% CI)		(7.4, 17.2)
p-value		<0.001
NNT*		8.1
Rescue medication within 24hrs		
Responders, n(%)	199 (29.2)	95 (14.2)
Difference from PBO		-15.0
(95% CI)		(-19.3, -10.7)
p-value		<0.001
NNT*		6.7
SPF from 2 to 24 hrs		
Responders, n(%)	38 (5.6)	105 (15.7)
Difference from PBO		10.1
(95% CI)		(6.9, 13.4)
p-value		<0.001
NNT*		9.9
Photophobia freedom		
Responders, n(%)	150/611 (24.5)	198/593 (33.4)
Difference from PBO		8.9
(95% CI)		(3.7, 13.9)
p-value		<0.001
NNT*		11.2
Phonophobia freedom		
Responders, n(%)	135/447 (30.2)	188/451 (41.7)
Difference from PBO		11.5
(95% CI)		(5.3, 17.7)
p-value		<0.001
NNT*		9.7

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	Placebo N=682	75 mg N=669
SPF 2 to 48 hours		
Responders, n(%)	37 (5.4)	90 (13.5)
Difference from PBO		8.1
(95% CI)		(4.9, 11.1)
p-value		<0.001
Nausea freedom		
Responders, n(%)	194/430 (45.2)	203/397 (51.0)
Difference from PBO		5.8
(95% CI)		(-0.9, 12.7)
p-value		0.090
NNT*		17.2

This table was adapted from Table 11-2 in the CSR for study 303
*NNT was calculated by the reviewer

Reviewer's comment: For the endpoints SPF at 24 and 48 hours, my recommendation would be to include one but not both of these endpoints. If the 48-hour endpoint is included, by definition this captures pain freedom at 24 hours as those patients who are sustained pain free at 48 hours were also sustained pain free at 48 hours. The migraine guidance recommends evaluating one of the two endpoints(24 or 48 hours) but not necessarily both. The data presented above looks more favorable at 24 hours than at 48 hours, and that would be my recommendation to include the endpoint at 24 hours. It is also worth noting that from 24 to 48 hours after dosing, a greater percentage of placebo-treated patients remained sustained pain free than did rimegepant-treated patients (37/38 vs 90/105)

Dose/Dose Response

N/A

Sensitivity Analyses Conducted on Study 303

Study 303 was initiated after the software data fix was in place, so sensitivity analyses regarding this issue were not required. The applicant did conduct a sensitivity analysis using LOCF (Table 34) and "complete case" i.e., observed data only (Table 35).

Table 34 Study 303: Sensitivity Analysis using LOCF

	Placebo N= 682	75 mg N= 669
Pain Freedom at 2 hours		
Responders, n(%)	77(11.3%)	145 (21.7%)

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Difference from PBO		10.4
(95% CI)	8.9, 13.7	18.6, 24.8
p-value		<0.0001

This is adapted from the CSR for study 303, table 14.2.1.1.4.1

Table 35 Study 303: 'Complete Case' Sensitivity Analysis

	Placebo N= 682	75 mg N=669
Pain Freedom at 2 hours		
Responders, n(%)	74/654 (11.3%)	142/649 (21.9%)
Difference from PBO		10.6%
(95% CI)	8.9, 13.7	18.7, 25.1
p-value		<0.0001

This table is adapted from the CSR for study 303, table 14.2.1.1.4.2

A for-cause audit was performed on site 002 and the applicant shared the results from this audit with the Division prior to the submission of the NDA. The Division recommended that the applicant conduct a sensitivity analysis that excluded site 002 from the primary efficacy analysis (Table 36).

Table 36 Study 303: Sensitivity Analysis excluding Site 002

	Placebo N= 676	75 mg N=655
Pain Freedom at 2 hours		
Responders, n(%)	72 (10.7%)	137 (20.9%)
Difference from PBO		10.2%
(95% CI)	8.3, 13.0	17.8, 24.0
p-value		<0.0001

This is adapted from the CSR from study 303, table 14.2.1.1.4.5

Reviewer's comment: The applicant-conducted sensitivity analyses support the conclusion of the primary efficacy analysis for pain freedom at 2 hours.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

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7.1.1. Primary Endpoints

For all three pivotal efficacy studies (301, 302, and 303), the applicant used the co-primary endpoints as outlined by the Migraine Guidance for Industry. These co-primary endpoints were pain freedom and absence of most bothersome symptom at 2 hours after dosing. These three studies were essentially identically designed. The treatment effect measured in each of the three pivotal studies was statistically significant for each of the co-primary endpoints for the 75 mg dose.

Table 37 Summary of Findings for the Co-Primary Endpoints for Studies 301, 302, and 303

	PBO 301	75 mg 301	PBO 302	75 mg 302	PBO 303	75 mg 303
Pain free at 2 hours (%)	14.2	19.2	12.0	19.6	10.9	21.2
Treatment effect (%)		5.0		7.6		10.3
Absence of MBS at 2 hours (%)	27.7	36.6	25.2	37.6	26.8	35.1
Treatment effect (%)		8.9		12.4		8.3

Reviewer created summary table

7.1.2. Secondary and Other Endpoints

Studies 301 and 302 contained the same 11 secondary endpoints and tested them in the same hierarchical order (Table 38). Study 303 contained the same 11 secondary endpoints and included an additional 10 secondary endpoints. All of the secondary endpoints for study 303 were significant except for freedom from nausea at 2 hours and pain relapse from 2 to 48 hours.

Table 38 Secondary Endpoints for Studies 301 and 302

	301 & 302 75 mg	303
Photophobia freedom	x	x
Phonophobia freedom	x	x
PR at 2 hours	x	x
Nausea freedom		
Rescue medication in 24 hours	y	x
SPF 2 to 24 hours	y	x
SPR 2 to 24 hours	y	x
SPF 2 to 48 hours	y	x
SPR 2 to 48 hours	y	x

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Pain relapse from 2 to 48 hours		
Ability to work/function normally	y	x

X= statistically significant
Y=nominally significant

The additional ten secondary endpoints for study 303 all reached statistical significance and were as follows:

-Sustained freedom from MBS from 2 to 24 hours
-Sustained normal functioning from 2 to 24 hours
-Sustained freedom from MBS from 2 to 48 hours
-Sustained normal functioning from 2 to 28 hours
-Functional disability at 90 minutes
-Pain relief at 90 minutes
-MBS freedom at 90 minutes
-Pain freedom at 90 minutes
-Pain relief at 60 minutes
-Functional disability at 60 minutes

I have included a summary table of the secondary endpoints that I think are appropriate for product labeling. I have included results of those endpoints that reached nominal significance as those endpoints reaching nominal significance were statistically significant in study 303. Absence of nausea did not reach statistical or nominal significance in any of the three studies. I suggest that this should be noted in product labeling.

Table 39 Summary of the Treatment Effect for Key Secondary Endpoints

	PBO 301	75 mg 301	PBO 302	75 mg 302	PBO 303	75 mg 303
Pain relief at 2 hours(%)	45.7	56.6	42.8	58.1	43.3	59.3
Treatment effect (%)		10.3		15.3		16.0
Freedom from functional disability	21.8	33.3	23.4	32.6	25.8	38.1
Treatment effect (%)		11.5		9.2		12.3
Rescue medication within 24 hrs	31.8	20.4	37.0	21.1	29.2	14.2
Treatment effect (%)		-11.3		-16.0		-15.0
SPF 2 to 24 hrs	8.1	14.0	7.1	12.3	5.6	15.7
Treatment effect (%)		5.9		5.2		10.1
Photophobia (%)	24.8	34.9	22.3	37.4	24.5	33.4

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Treatment effect (%)		10.1		15.1		8.9
Phonophobia (%)	30.9	38.6	26.8	36.7	30.2	41.7
Treatment effect (%)		7.7		9.9		11.5

Reviewer-created summary table

Reviewer's comment: At EOP2, the Division told the applicant that it was not necessary to 'spend alpha' on the description of the three individual migraine related symptoms. The Division indicated that inclusion of that information in the label would be descriptive. The applicant included these three symptoms high in the testing hierarchy for studies 301 and 302. Because the endpoint related to nausea freedom at 2 hours was not statistically significant, p-values for the analyses following the nausea endpoint could be considered exploratory. All of these endpoints following nausea (except pain relapse) had p-values <0.01 The applicant re-ordered the secondary endpoints for study 303, placing nausea lower on the list. In study 303, all secondary endpoints that were considered nominal in studies 301 and 302 reached statistical significance in study 303. Had the applicant followed our recommendation and not included the individual migraine symptoms in the testing hierarchy, then all the secondary endpoints for studies 301 and 302 (except pain relapse) would have been considered statistically significant rather than nominally significant.

7.1.3. Subpopulations

The applicant performed subpopulation analyses on pooled data for studies 301, 302, and 303. I have presented the applicant's results of the pooled analyses by age and sex, as well as my own analysis by BMI ≥30 kg/m².

Analyses Pooled by Age

The applicant conducted pooled analyses by age for patients ≥65 years for pain freedom at 2 hours and absence of most bothersome symptom (Table 40). It appears that there is no treatment effect in patients over age 65 on the co-primary endpoint pain freedom at 2 hours. For absence of MBS at 2 hours, the treatment effect is diminished but relatively maintained.

Table 40 Pooled Analyses of the Co-Primary Endpoint Efficacy Results

	Placebo N=1758	75 mg N=1749
Pain Freedom at 2 hours		
N1 (patients ≥65)	50	35
Responders, n(%)	6 (12.0%)	4 (11.4%)
Treatment effect (%)		-0.6%

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Absence of MBS at 2 hours		
N1 (patients ≥65)	50	35
Responders, n(%)	11 (22.0%)	10 (28.6%)
Treatment effect (%)		6.6%
Pain Freedom at 2 hours		
N1 (patients <65)	1708	1714
Responders, n(%)	209 (12.2%)	347 (18.3%)
Treatment effect (%)		6.1%
Absence of MBS at 2 hours		
N1 (patients <65)	1708	1714
Responders, n(%)	457 (26.8%)	626 (36.5%)
Treatment effect (%)		9.7%

This table is adapted from Table 7 in the SCE

Reviewer's comment: The sample size for this analysis is very small and is not powered to detect a treatment effect in the patient population over age 65. However, it is still an interesting and somewhat concerning finding. A similar trend was found in the review of other CGRP receptor antagonists that no treatment effect was seen in the older population.

Analyses Pooled by Sex

The applicant conducted pooled analyses by sex for pain freedom at 2 hours and absence of most bothersome symptom. There is no therapeutic gain in male patients (Table 41).

Table 41 Pooled Analyses of the Co-Primary Endpoint Efficacy Results by Sex

	Placebo N (Males)=244 N (Females)=1514	75 mg N (Males)=238 N (Females)=1511
Pain Freedom at 2 hours		
Responders, n (%) Male	31 (12.8)	32 (13.9)
Treatment effect (%)		1.1
Responders, n (%) Female	184 (12.2)	319 (21.1)
Treatment effect (%)		8.9
Absence of MBS at 2 hours		
Responders, n (%) Male	65 (26.6)	79 (33.2)
Treatment effect (%)		6.6
Responders, n (%) Female	403 (26.7)	557 (36.9)
Treatment effect (%)		10.2

This table is adapted from Table 7 in the SCE

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Reviewer's comment: Again, this analysis was not powered to detect a treatment effect in the male population. However, it is still an interesting and somewhat concerning finding. A similar trend was found in the review of another CGRP receptor antagonist that no therapeutic gain was seen in the male population.

Analyses Pooled by BMI

I conducted an analysis of the co-primary endpoint of pain freedom at 2 hours on those patients who had a BMI ≥30 kg/m² and compared to those patients with a BMI <30 kg/m².

	Placebo	75 mg
Pain Freedom at 2 hours		
N1 (BMI ≥30 kg/m²)	807	826
Responders, n(%)	115 (14.3)	176 (21.3)
Treatment effect (%)		7%
Pain Freedom at 2 hours		
N1 (BMI <30 kg/m²)	894	878
Responders, n(%)	101 (11.2)	177 (20.1)
Treatment effect (%)		8.9

Reviewer created table from ISE ADAM dataset ADPAIN join with ADSL

Reviewer's comment: Treatment effect appears to be maintained in the obese patient population. This is an important finding since approximately 40% of the U.S. population is obese.

7.1.4. Dose and Dose-Response

The applicant included only one dose in the pivotal studies. In a phase 2, dose-finding study the 150 mg dose was found to be the most effective (32.9% of patients achieving pain freedom at 2 hours). However, the dose response was mostly flat as 75 mg, and 300 mg doses both showed similar response rates (31.4% and 29.7%) on pain freedom at 2 hours.

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Figure 2 Study CN170003: Percentage of Patients Pain Free at 2-Hours

This figure was taken from Marcus et al. 2014.

7.1.5. Onset and Durability of Efficacy Effects

Onset of Effect

The onset of effect appears to begin at about 1.5 hours (90 minutes) after the initial dose was taken. This roughly corresponds to the Tmax. The applicant conducted an analysis on study 303 of pain freedom at 90 minutes postdose. In study 303, this analysis was statistically significant as compared to placebo. There were 15.1% of rimegepant- treated patients who were pain free at 90 minutes compared to 7.3% of placebo-treated patients (p <0.0001).

Durability of Effect

The applicant evaluated the secondary endpoint sustained pain freedom from 2 to 24 hours. Sustained pain freedom is defined as pain freedom with no administration of rescue medication, and with no occurrence of a headache of any intensity. This endpoint was nominally significant in studies 301, and 302 and statistically significant in study 303. Approximately 6-8% of placebo-treated patients experienced sustained pain freedom at 24 hours compared to 12-16% of rimegepant-treated patients.

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7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The applicant attempted to capture the population that will most likely benefit from the use of rimegepant. However, there are few issues that may arise in the postmarketing setting when the drug becomes more widely available that were not captured in the development program. The development plan included some patients over age 65. The limited efficacy data on this population suggests that there is no therapeutic gain in patients age 65 and older. There is limited data to inform on the safety of the product in patients over age 65. This could potentially alter the risk-benefit ratio in patients over age 65.

7.3. Integrated Assessment of Effectiveness

The applicant has submitted enough evidence to meet the statutory evidentiary standard. Studies 301, 302, and 303 all provide evidence that 75 mg of rimegepant is an effective dose for the acute treatment of migraine. Studies 301 and 302 demonstrated the efficacy of the tablet formulation, and study 303 demonstrated the efficacy of the ODT formulation. In all three studies, the applicant demonstrated statistical significance on the co-primary endpoints pain freedom at 2 hours, and absence of MBS at 2 hours.

The efficacy of rimegepant is also supported by the results of several key secondary endpoints. For studies 301 and 302, statistical significance was reached on the following endpoints: pain relief at 2 hours, photophobia freedom at 2 hours, and phonophobia freedom at 2 hours. Nominal significance was reached on endpoints related to sustain pain freedom, sustained pain relief, use of rescue medication, and functional disability at 2 hours.

In studies 301 and 302, the applicant failed to reach statistical significance on the absence of nausea at 2 hours. Because of the order of the secondary endpoints, further testing of endpoints following nausea resulted in nominally significant p-values. In study 303, the secondary endpoints were reordered in a such a way that nausea was tested nearly last. This resulted in nearly all secondary endpoints reaching statistical significance (except for absence of nausea and pain relapse). Had the sponsor incorporated our feedback at EOP2 and not included the individual migraine symptoms in the testing hierarchy, the secondary endpoints related to sustained pain freedom, sustained pain relief, use of acute medications, and ability to function would have reached statistical significance in studies 301 and 302.

For the purposes of product labeling, I recommend inclusion of results of the co-primary endpoints for all three studies. From study 303, I recommend including the results for the endpoints related to pain relief, sustained pain freedom, use of rescue medication, and functional disability.

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Subgroup analyses suggest absence of therapeutic gain in patients ≥ age 65, and male patients. While these analyses were not powered to detect a difference from placebo, the results are notable as similar trends were seen during the review other CGRP receptor antagonists.

From my review of the pivotal studies presented in section 6 and summarized in section 7, I recommend approval of the 75 mg (b) (4) ODT formulation of rimegepant for the acute treatment of migraine with and without aura.

8. Review of Safety

8.1. Safety Review Approach

The safety review includes studies 301, 302, 303, 201, and CN170003. The applicant has defined the safety population as any patient who received one or more doses of IP from these studies.

Table 42 Clinical Studies Contributing to the Integrated Review of Safety

Study	Dose	Patients in double-blind safety set	Patients in open-label safety set
301	Placebo or 75 mg	Placebo (549), Rimegepant (546)	N/A
302	Placebo or 75 mg	Placebo (540), Rimegepant (543)	N/A
303	Placebo or 75 mg ODT	Placebo (693), Rimegepant (682)	N/A
CN170003	Placebo, sumatriptan 100 mg, rimegepant 10 mg, 25 mg, 75 mg, 150 mg, 300 mg, 600mg	Placebo (209), Rimegepant 10 mg (72), Rimegepant 25 mg (62), Rimegepant 75 mg (86), Rimegepant 150 mg (86), Rimegepant 300 mg (112), Rimegepant 600 mg (84)	N/A
201	75 mg	N/A	1798*

*This number is inclusive of the 90-day safety update dated September 23, 2019, eCTD seq 0013

The applicant presented the safety analyses in the following pools. I numbered the pools as

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follows for clarity:

Group 1: single-dose studies involving patients treated with rimegepant 75 mg or placebo; studies 301, 302, 303, and CN170003
Group 1a: only the three single dose pivotal studies (301, 302, 303)
Group 2: single dose study involving patients treated with placebo, sumatriptan, and other rimegepant doses (CN170003)
Group 3: multiple-dose study (study 201)
Group 4: pools 1 and 3 combined for exposure calculations
Group 5: pooled safety data in healthy volunteers

In this review, I summarize information from the applicant's materials, and supplement them with analyses that I conducted using data from the Summary of Clinical Safety (SCS), the Integrated Summary of Safety (ISS), the 90-day safety update, and the applicant provided datasets. The applicant's datasets were initially analyzed by the Office of Computational Science (OCS) JumpStart team.

The analyses that I performed on the applicant-provided datasets were carried out using the JMP software program. The primary safety data comes from pooled data from the three pivotal studies. Analyses were conducted primarily on Group 1a and Group 3. For the adverse event section in this review, I focus on events reported from all the migraine studies to identify commonly reported events and infrequent events of potential concern. I present data from the controlled phase of the migraine studies to identify relative differences in risk by treatment for drug-relatedness.

Anticipated areas of interest for the safety review

The safety concerns that are theoretically associated with CGRP inhibition are cardiovascular, cerebrovascular, peripheral vascular, and gastrointestinal. CGRP is a potent vasodilator. The theoretical concern is that CGRP receptor antagonism during times of ischemia may prevent compensatory vasodilatation from occurring. Another potential safety concern is hepatic injury. This concern has arisen with small molecule CGRP receptor inhibitors that were previously in development. Drugs from the 'gepant' class of CGRP receptor antagonists have been reported to cause elevated liver enzymes in the setting of daily use (Yao et al).

Design of the Open-Label Study 201

In the open-label study for rimegepant, the applicant enrolled three cohorts, all of which received 75 mg of rimegepant. Cohort 1 enrolled patients with a migraine history of two to eight migraines per month. Cohort 2 enrolled patients with a migraine history of nine to fourteen migraines per month. In Cohorts 1 and 2, patients were instructed to treat their

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migraines as needed, using up to one dose of rimegepant per day. Cohort 3 instructed patients to take rimegepant every other day (EOD) regardless of whether they experienced a migraine. In Cohort 3, on days that were not already scheduled for dosing, patients could take an additional dose of rimegepant if needed to treat a migraine.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

At the time of the initial filing, a total of 5553 people took at least one dose of rimegepant during the development program. Among those, 3397 unique people received at least one dose of 75 mg.

Table 43 Safety Population, Size, and Denominators for Rimegepant Across Studies

Safety Database for Rimegepant		
Clinical Trial Groups	Rimegepant	Placebo
Healthy subjects	285	62
Controlled trials*	1857	1991
Uncontrolled trials	1798	0
Group 1**	1857	1991
Group 1a	1789	1782
Group 3	1798	0

*inclusive of 75 mg dose from studies 301, 302, 303, and CN170003; **75 mg dose only

From the Division's perspective, as per the migraine guidance, to be counted in the long-term safety database, adult patients should treat, on average, a minimum of two migraine attacks per month. Study 201 provided the long-term safety data to meet this requirement (Table 44). This table is inclusive of the 90-day safety update.

Because of the concern for potential hepatotoxicity and because the original planned study to evaluate hepatotoxicity was not conducted, the Division requested that the applicant provide data in up to 600 patients at 6 months, and 300 patients at 1 year who treated on average 2 migraine attacks per month.

Table 44 Study 201: Overall Extent of Exposure Per Migraine Guidance

	75 mg
≥3 months intermittent treatment	1508

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≥6 months intermittent treatment	1131
≥12 months intermittent treatment	863

To be included in this table, a patient needed to treat on average ≥2 migraine attacks per month
This table is adapted from the applicant's IR response dated August 9, 2019, eCTD seq no. 0006.

Table 45 shows the number of patients who treated a given average number of attacks per month during study 201 regardless of the length of time spent in the study. Table 46 is a subset of Table 45 and only includes the subset of patients who had one-year exposure (defined by the applicant as ≥51 weeks in the study). Table 47 is a reviewer-created table that shows the number of patients who treated a given number of migraine attacks monthly for at least one year (defined as ≥ 51 weeks). Table 48 shows the number of patients who treated a maximum given number of attacks in at least one month of treatment with rimegepant.

Table 45 Study 201: Distribution of Patients by Average Number of Attacks Treated per Month

Average number of attacks per month	75 mg N=1798 n(%)
0	4 (0.2)
>0 and <2	126 (7.0)
≥2 and <4	418 (23.2)
≥4 and <6	461 (25.6)
≥6 and <8	317 (17.6)
≥8 and <10	187 (10.4)
≥10 and <12	124 (6.9)
≥12 and <14	76 (4.2)
≥14	85 (4.7)

This table was adapted from an IR response dated November 13, 2019 eCTD seq no 0019.

Table 46 Study 201: Distribution of Patients by Average Number of Attacks Treated per Month with at Least One Year of Exposure

Average number of attacks per month	75 mg N=909 n(%)
>0 and <2	46 (5.1)
≥2 and <4	204 (22.4)
≥4 and <6	248 (27.3)

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≥6 and <8	176 (19.4)
≥8 and <10	84 (9.2)
≥10 and <12	66 (7.3)
≥12 and <14	45 (5.0)
≥14	40 (4.4)

This table was adapted from an IR response dated January 9, 2020, eCTD seq no 0031

Table 47 Study 201: Distribution of Patients by Average Number of Attacks Treated per Month with at Least One Year of Exposure

Average number of attacks per month	75 mg
≥2	862
≥3	775
≥4	658
≥5	536
≥6	412
≥7	310
≥8	236
≥9	188
≥10	151
≥11	112
≥12	85
≥13	58
≥14	40
≥15	27
≥16	17
≥17	10
≥18	7
≥19	6
≥20	6
≥21	5
≥22	5
≥23	4
≥24	4
≥25	3
≥26	3
≥27	2

Reviewer created table from dataset ADEXD. This table was created by identifying patients treated for 1 year (where PARAMCD=LTTDUR and AVALC ≥51) and dividing cumulative rimegepant exposure (where PARAMCD=CUMEXP) by number of months (in 4-week intervals) in long-term safety study.

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Table 48 Distribution of Patients by Maximum Number of Attacks Treated in One Month

Maximum number of attacks per month	75 mg N=1798 n(%)
0	4 (0.2)
>0 and <2	17 (0.9)
≥2 and <4	105 (5.8)
≥4 and <6	257 (14.3)
≥6 and <8	318 (17.7)
≥8 and <10	303 (16.9)
≥10 and <12	241 (13.4)
≥12 and <14	151 (8.4)
≥14	402 (22.4)

This table was adapted from an IR response dated November 13, 2019 eCTD seq no 0019.

Reviewer's comment: The applicant has proposed that dosing of rimegepant should be labeled 75 mg (b) (4) *The product is intended for chronic intermittent usage, not* (b) (4) *as this statement implies.* (b) (4)

Given the concern for medication overuse (MO) in patients using acute migraine medications, it would be prudent to limit the use of rimegepant to a frequency below which MO is known to develop. For triptans this threshold is around 10 migraines per months and for NSAIDs this threshold is considered to be around 15 days per month. I recommend a statement in the label, "The safety of treating more than 15 migraines a month has not been established."

8.2.2. Relevant characteristics of the safety population:

Migraine occurs more commonly in women than in men. The prevalence of the disease peaks in the fourth decade of life. The demographic characteristics in the rimegepant development program are not entirely representative of the intended treatment population. Migraine is more prevalent in women than men (3:1), but the ratio in these studies of women to men is on the order of 6:1 or 7:1. The racial distribution of the study population is similar to the U.S. population (https://www.census.gov/quickfacts/fact/table/US/PST045218) with the exception of Asians being somewhat underrepresented. The age of patients enrolled in the studies was appropriate. The applicant allowed patients age 18 and older to enroll with no fixed cap. This allowed for enrollment of patients up to age 84. However, the selection criteria for the migraine studies resulted in a relatively healthy population. The migraine studies excluded patients with the following disorders: recently diagnosed cardiovascular disease including

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ischemic heart disease, coronary artery disease, and cerebral ischemia; major psychiatric conditions, pain syndromes, or other significant neurological disorders. Patients with myocardial infarction, acute coronary syndrome, percutaneous coronary intervention, cardiac surgery, stroke, or transient ischemic attack during the 6 months prior to screening were also excluded. This may limit the generalizability of the safety data to the larger population when considering that postmarketing use will be much less restrictive. This also may have limited the number of patients over age 65 who were eligible to enroll.

The demographic characteristics of the patients who received at least one dose of IP in the three pivotal studies are presented below (Table 49).

Table 49 Group 1a: Summary of Demographic Characteristics for the Safety Analysis Set

Demographic Parameters	Placebo	75 mg
	N= 1782 n (%)	N= 1771 n (%)
Sex		
Male	248 (13.9)	242 (13.7)
Female	1534 (86.1)	1529 (86.3)
Age		
Mean years (SD)	40.7 (12.1)	40.8 (12.1)
Median (years)	39.9	39.7
Min, max (years)	18, 84	18, 76
Age Group*		
18 to <40	896 (50.3)	888 (50.1)
≥40 to <65	834 (46.8)	847 (47.8)
≥65	52 (2.9)	36 (2.0)
Race		
White	1378 (77.3)	1322 (74.6)
Black or African American	331 (18.6)	365 (20.6)
Asian	34 (1.9)	23 (1.3)
American Indian or Alaska Native	13 (0.7)	9 (0.5)
Native Hawaiian or Other Pacific Islander	5 (0.3)	19 (1.1)
Multiple	21 (1.2)	31 (1.8)
Ethnicity		
Hispanic or Latino	292 (16.4)	254 (14.3)
Not Hispanic or Latino	1490 (83.6)	1517 (85.7)
BMI (kg/m^2)		

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Mean (SD)	30.7 (8.1)	30.8 (7.9)
Median	29.3	29.5
Min, Max	15.1, 75.7	14.7, 67.6

This table was adapted from the ISS appendix table 1.3.1D
*This was calculated by the reviewer

Table 50 Study 303: Summary of Demographic Characteristics for the Safety Analysis Set

Demographic Parameters	Placebo	75 mg
	N= 693 n (%)	N= 682 n (%)
Sex		
Male	104 (15.0)	104 (15.2)
Female	589 (85.0)	578 (84.8)
Age		
Mean years (SD)	40.0 (11.8)	40.3 (12.1)
Median (years)	38.9	39.7
Min, max (years)	18, 71	18, 75
Age Group		
18 to <40	375 (54.1)	348 (51.0)
≥40 to <65	301 (43.4)	322 (47.2)
≥65	17 (2.5)	12 (1.8)
Race*		
White	527 (76.0)	506 (74.4)
Black or African American	129 (18.6)	143 (21.0)
Asian	19 (2.7)	9 (1.3)
American Indian or Alaska Native	4 (0.6)	4 (0.6)
Native Hawaiian or Other Pacific Islander	5 (0.7)	11 (1.6)
Multiple	9 (1.3)	7 (1.0)
Ethnicity		
Hispanic or Latino	137 (19.8)	118 (17.3)
Not Hispanic or Latino	556 (80.2)	564 (82.7)

Reviewer created table from study 303 dataset ADSL
*Race information was missing for two patients in the rimegepant arm

8.2.3. Adequacy of the Safety Database

The overall exposure to rimegepant fulfills the minimum ICH guidelines for repeated intermittently used medications (i.e., 1500 exposed overall, 300 to 600 exposed for 6 months,

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and 100 exposed for one year). The applicant has also fulfilled the requirements as outlined in the Guidance for Industry- Migraine: Developing Drugs for Acute Treatment (Table 44). The guidance recommends that applicants should obtain safety data on at least 100 patients treating, on average, at least two migraine attacks per month for one year with a substantial experience at the highest dose and highest frequency of administration proposed for marketing. At EOP2, the applicant had been asked to include at least 600 patients at 6 months and 300 patients at 12 months treating on average two migraines per month. The applicant has also fulfilled this requirement. The median BMI is reflective of the U.S. population. Major cardiovascular disease, which will be discussed in detail in section 8.5.1, is not represented. The applicant followed patients for one week after receiving rimegepant. The half-life of the drug is approximately 11 hours. This should adequately capture AEs while the drug is present in the body.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Biohaven's datasets were assessed by the Office of Computational Science using the JumpStart program.

I had some difficulty using the applicant's datasets. The patients who were in studies 301, 302, and 303 that continued into study 201 had two USUBJIDs. This made identifying unique patients difficult at times.

Reviewer's comment: The applicant should have used the same USUBJID in all studies and in ISS combined datasets could have used STUDYID to identify in which study a particular AE, lab value, etc. belonged.

8.3.2. Categorization of Adverse Events

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

Non-serious adverse events were followed until conclusion or stabilization. Follow-up was required for non-serious AEs that caused interruption or discontinuation of IP.

Serious adverse events (SAEs) were defined as any event that results in any of the following

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outcomes: death, life-threatening, inpatient hospitalization, persistent or significant disability/incapacity, or a congenital birth defect. Other events were considered SAEs if they required medical or surgical intervention to prevent one of the outcomes listed above. The applicant did not consider visits to the emergency room as SAEs.

8.3.3. Routine Clinical Tests

In studies 301, 302, and 303, blood and urine samples were collected at screening and at the end of treatment visit which was seven days after treatment.

In study 202, laboratory testing including LFTs were obtained at the screening visit, the baseline visit, and then monthly until termination of the study. Urinalysis was done at the baseline visit and then monthly until termination of the study.

Table 51 Clinical Laboratory Tests

Chemistry	Sodium, potassium, chloride, bicarbonate, calcium; glucose, BUN (urea), serum creatinine, uric acid, ALT, AST, alkaline phosphatase, LDH, total protein, albumin, total bilirubin, direct bilirubin, indirect bilirubin, creatine kinase
Hematology	Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelets
Urinalysis	pH, specific gravity, ketones, nitrites, urobilinogen, leukocyte esterase, protein, glucose, microalbuminuria and blood. If blood, protein or leukocytes are positive, reflex microscopic examination
Urine drug screen	Screening for drugs of abuse
Lipid panel	Cholesterol, LDL, HDL, triglycerides (screening only)

The applicant used the Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE) to grade the laboratory data.

Vital Signs

Vital sign measurements, including sitting blood pressure, sitting heart rate, respiratory rate, body temperature, body weight, and height were collected. In studies 301, 302, and 303, vital signs were collected at screening, baseline, and the end of treatment visits. In study 201, vital signs were collected at screening, baseline, then monthly, and at the safety follow-up visit.

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8.4. Safety Results

8.4.1. Deaths

There were no deaths during the clinical development program for rimegepant.

8.4.2. Serious Adverse Events

The double-blind placebo-controlled data was examined for imbalances between placebo-treated patients and rimegepant-treated patients. There were 2273 patients in Group 1 who were treated with rimegepant and 1991 placebo-treated patients. There were 4 SAEs reported by rimegepant-treated patients (pneumonia, post lumbar puncture syndrome, stress cardiomyopathy, and back pain) and 3 SAEs reported in patients taking placebo (chest pain, colitis, and urinary tract infection).

There were 1798 patients in Group 3, which consisted of patients in the long-term safety study 201. In Group 3, there were 66 SAES experienced by 56 patients (Table 52).

Table 52 Group 3 SAEs: Open-Label Experience

MedDRA System Organ Class Serious Adverse Event (Preferred Term)	75 mg N=1798 n(%)
Blood and Lymphatic System Disorders	1 (0.1)
Anemia	1 (0.1)
Cardiac Disorders	1 (0.1)
Atrial fibrillation	1 (0.1)
Gastrointestinal Disorders	8 (0.4)
Appendiceal mucocele	1 (0.1)
Colitis ischemic	1 (0.1)
Constipation	2 (0.1)
Diabetic gastroparesis	1 (0.1)
Gastritis	1 (0.1)
Pancreatitis acute	1 (0.1)
Peritoneal hemorrhage	1 (0.1)
General and Administration Site	2 (0.1)
Chest pain	1 (0.1)
Pyrexia	1 (0.1)
Hepatobiliary Disorders	2 (0.1)
Cholecystitis	1 (0.1)
Cholecystitis chronic	1 (0.1)

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MedDRA System Organ Class Serious Adverse Event (Preferred Term)	75 mg N=1798 n(%)
Infections and infestations	15 (0.8)
Appendicitis	4 (0.2)
Cellulitis	1 (0.1)
Diverticulitis	1 (0.1)
Gastroenteritis	1 (0.1)
Influenza	1 (0.1)
Mastitis	1 (0.1)
Pneumonia	2 (0.1)
Sepsis	4 (0.2)
Injury, poisoning and procedural complications	3 (0.2)
Accidental overdose	3 (0.2)
Musculoskeletal and connective tissue disorders	5 (0.3)
Arthritis/osteoarthritis	4 (0.2)
Chest pain (musculoskeletal)	1 (0.1)
Neoplasms benign, malignant, and unspecified	3 (0.2)
Colon cancer	1 (0.1)
Invasive ductal breast carcinoma	1 (0.1)
Uterine leiomyoma	1 (0.1)
Nervous system disorders	5 (0.3)
Hemiplegia	1 (0.1)
Headache/migraine/migraine with aura/hemiplegic migraine	4 (0.2)
Psychiatric disorders	7 (0.4)
Bipolar disorder/bipolar I disorder	1 (0.1)
Depression	1 (0.1)
Post-traumatic stress disorder	1 (0.1)
Suicidal ideation	3 (0.2)
Renal and urinary disorders	2 (0.1)
Nephrolithiasis	2 (0.1)
Reproductive system and breast disorders	3 (0.2)
Dysmenorrhea/menorrhagia	2 (0.1)
Hemorrhagic ovarian cyst	1 (0.1)
Respiratory, thoracic, and mediastinal disorders	6 (0.3)
Asthma	2 (0.1)
Pulmonary embolism	4 (0.2)
Skin and subcutaneous tissue disorders	1 (0.1)
Lipodystrophy acquired	1 (0.1)

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MedDRA System Organ Class Serious Adverse Event (Preferred Term)	75 mg N=1798 n(%)
Vascular disorders	2 (0.1)
Aortic dissection	1 (0.1)
Deep vein thrombosis	1 (0.1)
# of SAEs	66
# of patients	56

Narratives of Selected SAEs

Aortic dissection

Patient (b) (6)
This 46-year-old female was participating in the open-label treatment study 201 when she experienced chest pain, dizziness, and 'blacking out'. She was taken to the emergency room and hospitalized for an aortic dissection. She underwent emergent surgery for a Stanford Type A (ascending) aortic dissection ((b) (6)). At screening the patient's blood pressure was 149/91. At the week 12 visit ((b) (6)), the patient's blood pressure was 150/105 mmHg and was coded as a mild adverse event of hypertension. The patient took 5 to 7 doses of rimegepant per month from (b) (6). Her last dose of rimegepant prior to the aortic dissection was (b) (6), which was about 5 days prior to the onset of symptoms. The patient was a smoker with a BMI of 28.4 kg/m².

Reviewer's comment: Risk factors for the development of an aortic dissection include hypertension, atherosclerosis, hypercholesterolemia, smoking, trauma, and family history (Al'Aref et al. 2015). The patient was a smoker which is a risk factor for development of a dissection. She also had elevated blood pressure upon entry into the study but did not carry a diagnosis of hypertension when she was enrolled. The patient was young, and female which is unusual for patients with aortic dissection, although the average age is slightly lower in patients with ascending aortic dissection. For this case, I cannot completely exclude the role of rimegepant in the development of the aortic dissection. Hypertension is a risk factor for development of aortic dissection and there is some suggestion that CGRP has a role in hypertension (Russell et al. 2014) although the understanding of its role is unclear. Cardiovascular safety will be discussed in more detail in section 8.5.

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Chest pain

Patient (b) (6)
This is a 36-year-old female who was participating in the open-label treatment study 201 when she presented to the emergency room with acute chest pain and weakness. She was found to have a hemoglobin of 7.0g/dL and a hematocrit of 26.6%. She was transfused 2 units of packed red blood cells and told to follow up with OB/GYN for treatment of anemia from heavy menstrual periods.

Reviewer's comment: The patient's chest pain is unlikely to be related to rimegepant.

Thromboses

1. Patient (b) (6)

This is a 43-year-old female who was participating in the open-label treatment study 201 when she developed right leg pain. The patient was seen in the emergency room and underwent an ultrasound of the right lower extremity which showed a DVT in the common femoral, femoral, and popliteal veins. The patient had previously had an IVC filter placed and had been on warfarin for treatment of a DVT. She had several episodes of DVT in the past. Her father had a history of blood clots as well. The patient was started on apixaban and discharged. She had received three to nine tablets per month of rimegepant for about 9 months. Her last dose was nine days prior to developing the DVT, and she took on additional dose after the DVT prior to being withdrawn from the study.

2. Patient (b) (6)

This 42-year-old female was participating in the open-label treatment study 201 when she presented to the ER with dyspnea. CT angiography of the chest showed evidence of bilateral lower lobe pulmonary emboli. The patient was admitted to the hospital and started on enoxaparin. She was eventually switched to rivaroxaban. An ultrasound of the lower extremities showed no evidence of DVT. The patient had a family history of DVT and pulmonary embolism, but no personal history of either.

3. Patient (b) (6)

This 26-year-old female was participating in the open-label treatment study 201 when she presented to the emergency room with short of breath. She was diagnosed with bilateral pulmonary embolism and started on apixaban. She had a history of pulmonary embolism one year prior. Her concomitant medication at the time of the diagnosis of the pulmonary embolism was ethinyl estradiol/norelgestromin.

Reviewer's comment: This patient was on oral contraceptives at the time she experienced the pulmonary embolism. Use of OCPs is a risk factor for development of blood clots.

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4. Patient (b) (6)

This 43-year-old-female was participating in the open-label treatment study 201 when she developed chest pain. She was diagnosed with bilateral pulmonary emboli and admitted to the ICU. She had been diagnosed 18 months previously with a DVT and pulmonary embolism.

5. Patient (b) (6)

This 36-year-old female with a history of coagulopathy and deep vein thrombosis was participating in the open-label treatment study 201 when she developed right sided neck pain. She was seen in the ER and underwent an ultrasound that showed a partially occlusive right jugular vein. Five days later a repeat ultrasound showed no evidence of thrombosis.

6. Patient (b) (6)

This 31-year-old female was participating in the open-label treatment study 201 when she developed blood clots in the right arm. The patient had taken rimegepant 7 times from (b) (6) through (b) (6). She was found to have the thrombosis on (b) (6), and was subsequently discontinued from rimegepant. The patient's concomitant medications included ethinylestradiol/norethisterone.

Reviewer's comment: This patient was on oral contraceptives at the time she experienced the pulmonary embolism. Use of OCPs is a risk factor for development of blood clots.

Ischemic colitis

Patient (b) (6)

This 64-year-old female with a history of Crohn's disease was participating in study 201 when she experienced lower abdominal pain with watery diarrhea and rectal bleeding. CT scan showed colitis of a contiguous segment of the mid to distal transverse, descending, and proximal sigmoid colon. The patient underwent colonoscopy which showed moderate to severe inflammation of the mid-sigmoid through the mid-transverse colon with ulceration, erythema, and edema. Biopsy showed focal active colitis with mucosal surface erosion and acute inflammatory exudate in the distal transverse and descending colon consistent with ischemic colitis. Rimegepant was discontinued. The patient had been in the study for 15 weeks and had taken an average of 11 tablets per 4-week period during the study. Her last dose of rimegepant was the day prior to her presentation to the emergency room.

Reviewer's comment: I cannot exclude a role for rimegepant in this case. Theoretically concerns with CGRP antagonists include increased risk of gastric ulcer, bowel ischemia, and obstruction as CGRP has known roles in blood flow, inflammation, motility, and secretion into the colon. The patient has a history of Crohn's disease. Cases of ischemic colitis can mimic conditions such

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as flares of Crohn's or ulcerative colitis. However, the gastroenterology consultant in this case felt that the patient's case was likely ischemic colitis.

Constipation

1. Patient (b) (6)

This 29-year-old female was participating in the open-label study 201 when she presented to the ER with right lower quadrant abdominal pain. She had an unremarkable CT scan of the abdomen and pelvis. Abdominal and transvaginal ultrasounds were normal. She was treated with IV fluids, ondansetron, and morphine. The day following discharge the patient had a bowel movement. An SAE of constipation was then reported. The patient continued in the study and took an additional 12 doses of rimegepant without further reports of constipation.

Reviewer's comment: It is not clear if constipation was in fact the cause of the patient's abdominal pain. I cannot completely exclude the role of rimegepant in the development of constipation. However, the patient was able to continue on rimegepant without further difficulty.

2. Patient (b) (6)

This 54-year-old-female who was participating in the open-label study when she experienced AEs of 'ulcerative colitis', 'gastritis', and 'colonic inertia'. She took her first dose of rimegepant on (b) (6). The AE of ulcerative colitis was reported from (b) (6) through (b) (6) She then experienced an AE of gastritis from (b) (6), through (b) (6) (b) (6) She continued on rimegepant and then experienced the AE 'colonic inertia' on (b) (6) (b) (6). She had taken rimegepant for 19 out of 30 days prior to this AE with the last dose being two days prior. The patient was hospitalized on (b) (6) and underwent a total abdominal colectomy with ileorectal anastomosis. She continued in the study and took the last dose of rimegepant on (b) (6). She was reported to have a history of recurrent constipation.

Reviewer's comment: I cannot rule out the role of rimegepant in the development of the patient's colonic inertia. The patient had a long history of constipation. Endogenous CGRP is known to have a role in blood flow and motility in the colon. Other CGRP receptor antagonists have been shown to cause constipation or lead to more serious in outcomes especially in those pre-disposed to constipation. 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.

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Cardiomyopathy

Patient (b) (6)

This 50-year-old female was participating in the phase 2 study CN170003 when she developed chest pain under the left breast. She was admitted to the hospital for work-up. She underwent ECG which was reported as normal. She had a chest x-ray, and had troponins measured which were normal as well. She underwent cardiac catheterization which was normal as well without any evidence of blockage of the coronary arteries. She was given the diagnosis of Takotsubo's cardiomyopathy (broken heart syndrome) secondary to the recent death of her mother. The event occurred 8 days after the single dose of rimegepant 150 mg was taken. The event was reported as resolved about one week after the diagnosis was made.

Reviewer's comment: It is not clear that this patient actually had Takotsubo's cardiomyopathy. The patient had normal troponins and a normal cardiac catheterization. It is unlikely that the patient's chest pain was caused by rimegepant as it occurred 8 days after the single dose was taken.

Review of Designated Medical Events

I searched the ISS database for DMEs using the MedDRA-Based Adverse Event Diagnostics (MAED) software. The following PTs for DMEs were found in rimegepant-treated patients: anaphylactic reaction, drug-induced liver injury, and acute pancreatitis.

Elevated liver enzymes

1. Patient (b) (6)

This 43-year-old-female was participating in study 201 when she presented to the ER with nausea and abdominal pain. Her last dose of rimegepant was the day prior to presentation to the ER. She underwent CT scan of the abdomen and pelvis which was reported as showing "no acute changes". Initial LFTs in the ER were normal. She was diagnosed with GERD and an acute urinary tract infection which was treated with nitrofurantoin. She was given ketorolac IV, morphine IV, ondansetron IV, and promethazine IV in the ER. The following day she was seen by the PI for the study who felt the patient was constipated and prescribed two bottles of magnesium citrate. The patient improved after having a bowel movement. Labs that day showed markedly elevated ALT (27xULN) and AST (34xULN) with a normal Tbili. LFTs normalized 9 days later. This case was coded as drug-induced liver injury.

Reviewer's comment: This case is not consistent with Hy's Law as there was no concomitant elevation in the bilirubin. The patient was started on nitrofurantoin which considered by LiverTox, Clinical and Research Information on Drug-Induced Liver Injury provided by the NIH as

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one of the most common causes of drug-induced liver injury.

2. Patient (b) (6)

This 52-year-old-male was participating in study 201 when he experienced elevated ALT and TBili. The patient had been taking an average of 17 tablets of rimegepant per 4-week period for 22 weeks. The patient had elevated ALT at screening (59 U/L) which normalized at a repeat test (34 U/L). On (b) (6), he experienced elevated AST and ALT with normal TBili. Rimegepant was discontinued with the last dose taken on (b) (6) Follow up LFTs on (b) (6) showed a still elevated AST and ALT with normal TBili. The highest ALT reached was 5.8xULN with a normal Tbili. The patient experienced an ALT≥2.5xULN with a TBili ≥2x ULN at 43 days (b) (6)) after the last dose of rimegepant was taken. Tbili normalized on (b) (6) but ALT remained elevated (1.3 x ULN). The patient had a diagnosis of ulcerative colitis and had been taking mercaptopurine for this diagnosis.

Reviewer's comment: The patient had an ALT ≥3x ULN, and a Tbili ≥2x ULN. However, these elevations never occurred simultaneously. The patient was taking mercaptopurine for ulcerative colitis and had a three-year history of intermittently elevated AST and ALT. According to LiverTox, Clinical and Research Information on Drug-Induced Liver Injury provided by the NIH, mercaptopurine is well known cause of clinically apparent liver injury. This patient's elevated liver enzymes are unlikely to be secondary to rimegepant. The patient had another etiology that potentially caused the elevated liver enzymes.

<u>Anaphylaxis/Hypersensitivity</u>

1. Patient (b) (6)

This 39-year-old female was participating in the open-label treatment study 201 when she experienced hives on (b) (6) The patient had taken 6 doses of rimegepant in (b) (6) with the last dose on (b) (6) She was also started on sertraline on (b) (6) The investigator thought the hives were related to the sertraline, so this was discontinued. She was treated with oral prednisone and the drug hypersensitivity was considered resolved on (b) (6) She continued on rimegepant.

This patient was treated for two asthma exacerbations during her treatment with rimegepant in the open-label study. She was also reported to have an AE of anaphylaxis "of unknown etiology" on (b) (6) for which she was treated with prednisone for 5 days. She continued on rimegepant after both asthma exacerbations and the AE of anaphylaxis for four additional months. She received 58 additional doses of rimegepant during that time.

2. Patient (b) (6)

This 30-year-old female was participating in study 303. She took a single dose of rimegepant on

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(b) (6). On (b) (6), she presented to the ER with difficulty breathing and a severe maculopapular rash. The patient received diphenhydramine 50 mg and oral prednisone 10 mg for the rash. The rash resolved on (b) (6).

3. Patient (b) (6)

This 40-year-old female who received a single dose of 75 mg and experienced facial flushing on the same day. She was treated with oral diphenhydramine 25 mg. The following day the patient noted facial skin desquamation. No treatment was reported for this adverse event. The investigator attributed the skin desquamation to a new make-up the patient had started using.

4. Patient (b) (6)

This 68-year-old female was in the open-label treatment study 201 when she experienced swelling of the tongue. Her last dose of rimegepant had been 12 days prior to the onset of symptoms. She received treatment with diphenhydramine and symptoms resolved on the same day. She continued to receive rimegepant in the open-label study. She experienced a second episode of tongue swelling 7 days after her last dose. She did not receive any treatment for the second episode. The patient's episodes of tongue swelling were attributed to exposure to products that were known food allergens to the patient.

Reviewer's comment: Of the four cases described above, one case seems reasonable to attribute to the use of rimegepant. Two of the four cases have alternative causes for the hypersensitivity. In the remaining case, the patient remained on rimegepant and had further adverse events while on the drug, but it is less clear whether these were attributable to rimegepant.

<u>Acute pancreatitis</u>

Patient (b) (6)

This 54-year-old female was participating in open label study 201 when she presented to the ER with epigastric pain radiating to the chest and nausea. She was diagnosed with severe acute pancreatitis. Her last dose of rimegepant was 10 days prior to the episode. On admission her serum lipase was elevated to 1278U/L (range 13-60 U/L). A CT scan of the abdomen and pelvis showed mesenteric edema and a low attenuation focus in the pancreatic head. She was treated with IV fluids, and IV hydromorphone. The patient left the hospital against medical advice. She had a follow-up ultrasound four days after leaving the hospital that showed an unremarkable pancreas. Rimegepant was discontinued.

Reviewer's comment: The role of rimegepant in this case is unlikely given the lack of temporal association between the last dose and the onset of the pancreatitis.

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8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In the three phase 3 pivotal studies (Group 1a), there were no AEs leading to discontinuation. In Group 3, the long-term open-label study, there were 72 AEs reported by 56 patients that resulted in drug withdrawal (Table 53). The most frequent AEs leading to drug withdrawal were the following: dizziness (5), depression (3), suicidal ideation (3), and AST/ALT elevations (3).

There were three patients whose dose was reduced secondary to the following AEs: CPK increased, Crohn's disease aggravated, and upper respiratory tract infection.

Table 53 Group 3: Drug Withdrawn Due to Adverse Events

MedDRA System Organ Class Adverse Event (Preferred Term)	75 mg N=1798 n(%)
Cardiac disorders	3 (0.2)
Angina	1 (0.1)
Arrhythmia	1 (0.1)
Palpitations	1 (0.1)
Ear and labyrinth disorders	2 (0.1)
Vertigo	2 (0.1)
Gastrointestinal disorders	5 (0.3)
Abdominal pain	1 (0.1)
Ischemic colitis	1 (0.1)
Constipation	2 (0.1)
Acute pancreatitis	1 (0.1)
General and administration site	2 (0.1)
Fatigue	1 (0.1)
Pain	1 (0.1)
Hepatobiliary disorders	1 (0.1)
Hepatic cyst	1 (0.1)
Infections and infestations	3 (0.2)
Helicobacter gastritis	1 (0.1)
Hepatitis C	1 (0.1)
Sepsis	1 (0.1)
Injury, poisoning, and procedural complications	5 (0.3)
Abdominal injury	1 (0.1)
Back injury	1 (0.1)
Fall	1 (0.1)
Neck injury	1 (0.1)
Patella fracture	1 (0.1)

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MedDRA System Organ Class Adverse Event (Preferred Term)	75 mg N=1798 n(%)
Investigations	13 (0.7)
ALT increased	3 (0.2)
AST increased	3 (0.2)
CK increased	2 (0.1)
GGT increased	1 (0.1)
GFR abnormal	1 (0.1)
LFT increased	2 (0.1)
Transaminases increased	1 (0.1)
Musculoskeletal and connective tissue disorders	5 (0.3)
Arthralgia	2 (0.1)
Musculoskeletal pain	1 (0.1)
Osteoarthritis	1 (0.1)
Rotator cuff syndrome	1 (0.1)
Neoplasms benign, malignant, and unspecified	3 (0.2)
Colon cancer	1 (0.1)
Invasive ductal breast carcinoma	1 (0.1)
Malignant melanoma	1 (0.1)
Nervous system disorders	10 (0.6)
Dizziness	5 (0.3)
Headache	1 (0.1)
Hemiparesis	1 (0.1)
Idiopathic intracranial hypertension	1 (0.1)
Restless legs syndrome	1 (0.1)
Somnolence	1 (0.1)
Psychiatric disorders	11 (0.6)
Anxiety	2 (0.1)
Bipolar disorder	1 (0.1)
Depression	3 (0.2)
Tic disorder	1 (0.1)
Seasonal affective disorder	1 (0.1)
Suicidal ideation	3 (0.2)
Respiratory, thoracic, and mediastinal disorders	2 (0.1)
Oropharyngeal pain	1 (0.1)
Pulmonary embolism	1 (0.1)
Skin and subcutaneous tissue disorders	1 (0.1)
Alopecia	1 (0.1)
Vascular disorders	6 (0.3)

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MedDRA System Organ Class Adverse Event (Preferred Term)	75 mg N=1798 n(%)
Aortic dissection	1 (0.1)
Deep vein thrombosis/thrombosis	2 (0.1)
Hot flush	2 (0.1)
Hypertension	1 (0.1)

Reviewer created table from ISS dataset ADAE where AEACN= "drug withdrawn"

8.4.4. Significant Adverse Events

AEs Leading to Dose Interruption

In Group 3, there were 39 AEs reported by 31 patients that resulted in interruption of dosing (Table 54). The most frequent AEs leading to interruption of dosing were the following: arthritis/arthralgia, and abnormal LFTs.

Table 54 Group 3: Dosing Interrupted Due to Adverse Events

MedDRA System Organ Class Adverse Event (Preferred Term)	75 mg N=1798 n(%)
Cardiac disorders	1 (0.1)
Palpitations	1 (0.1)
Gastrointestinal disorders	3 (0.2)
Abdominal pain	1 (0.1)
Appendiceal mucocele	1 (0.1)
Peritoneal hemorrhage	1 (0.1)
General and administration site	2 (0.1)
Chest discomfort/chest pain	2 (0.1)
Infections and infestations	6 (0.3)
Bronchitis	1 (0.1)
Diverticulitis	1 (0.1)
Kidney infection	1 (0.1)
Pneumonia	1 (0.1)
Sinusitis	1 (0.1)
Tinea infection	1 (0.1)
Injury, poisoning, and procedural complications	1 (0.1)
Fibula fracture	1 (0.1)
Investigations	12 (0.7)

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MedDRA System Organ Class Adverse Event (Preferred Term)	75 mg N=1798 n(%)
ALT increased	1 (0.1)
AST increased	1 (0.1)
CK increased	2 (0.1)
Creatinine increased	2 (0.1)
GFR decreased	2 (0.1)
LFT abnormal	1 (0.1)
LFT increased	2 (0.1)
Urea increased	1 (0.1)
Musculoskeletal and connective tissue disorders	7 (0.4)
Arthralgia/arthritis	4 (0.2)
Back pain	1 (0.1)
Muscle spasms	1 (0.1)
Myalgia	1 (0.1)
Psychiatric Disorders	1 (0.1)
Depressed mood	1 (0.1)
Renal and urinary disorders	1 (0.1)
Nephrolithiasis	1 (0.1)
Reproductive system and breast disorders	2 (0.1)
Hemorrhagic ovarian cyst	1 (0.1)
Menorrhagia	1 (0.1)
Respiratory, thoracic, and mediastinal disorders	1 (0.1)
Pulmonary embolism	1 (0.1)
Skin and subcutaneous tissue disorders	1 (0.1)
Rash	1 (0.1)
Social circumstances	1 (0.1)
Aborted pregnancy	1 (0.1)

Reviewer created table where AEACN=dose interrupted

AEs by Intensity

The applicant categorized adverse events as mild, moderate, or severe in intensity. The applicant did not provide definitions for mild, moderate, or severe. The severity determination was made by the individual investigator.

In the double-blind treatment period and the open-label study, the majority of AEs were of mild intensity (Table 55).

Reference ID: 4566903

Table 55 Group 1a: AEs by Intensity in the DBTP

	Placebo		75 mg	
	AEs N=257 n(%)	Pts N=1782 n(%)	AEs N=282 n(%)	Pts N=1789 n(%)
Mild	165 (64.2)	120 (6.7)	180 (63.8)	143 (8.0)
Moderate	88 (34.2)	62 (3.5)	93 (33.0)	67 (3.7)
Severe	4 (1.6)	3 (0.2)	9 (3.2)	7 (0.4)

Reviewer created table from ISS dataset ADAE where SAFFL=Y, and APHASE ≠ SCREENING

Table 56 Group 3: AEs by Intensity in the Open-Label Study

	75 mg	
	AEs N= 3531 n(%)	Pts N= 1798 n(%)
Mild	1996 (56.5)	882 (49.1)
Moderate	1414 (40.0)	710 (39.5)
Severe	121 (3.4)	88 (4.9)

Reviewer created table from ISS dataset ADAE where SAFFL=Y, inclusive of 90-day safety update

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The most commonly reported TEAEs in the ISS database (Group 1) occurring in more than 1% of rimegepant-treated patients were various infections, and gastrointestinal symptoms (dyspepsia, nausea, vomiting, and epigastric pain). Some of these occurred at rates similar to placebo. I evaluated the rates for TEAEs in Group 1a, which includes the AEs from only the three pivotal efficacy studies, and report on the TEAEs that demonstrate an imbalance as compared to placebo (Table 58).

Table 57 Group 1: TEAEs in the DBTP occurring in **≥1%** of Rimegepant-Treated Patients

	Placebo N=1991	75 mg N=1857
Infection (all)	96 (4.8)	85 (4.6)
Dyspepsia, N/V, epigastric pain	35 (1.8)	40 (2.2)
URI, cold, flu-like illness	39 (2.0)	38 (2.0)
Nausea/vomiting	29 (1.5)	34 (1.8)
UTI	27 (1.4)	30 (1.6)

Reviewer created table from ISS dataset ADAE for Group 1 using FDA-created queries. This includes studies 301, 302, 303, and CN170003

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Table 58 Group 1a: TEAEs in the DBTP

	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)	13 (0.7)	1	7
Somnolence, fatigue, sedation	6 (0.3)	10 (0.6)	0	2

Reviewer-created table from ISS dataset ADAE where APHASE does not equal ≠ SCREENING, TRTNEMFL=Y
*includes the following PTs: gastrointestinal pain, dyspepsia, abdominal pain, abdominal distention, and abdominal discomfort
**includes the following PTs: gastrointestinal pain, abdominal pain, abdominal distension, and abdominal discomfort

Table 59 Study 303: TEAEs in the DBTP

	Placebo N=693	75 mg N=682	Risk Difference (%)
Dyspepsia, N/V, epigastric pain	7 (1.0)	15 (2.2)	1
UTI	11 (1.6)	14 (2.1)	0.5
Nausea/vomiting	6 (0.9)	13 (1.9)	1
Nausea	3 (0.4)	11 (1.6)	1
URI, cold, flu-like illness	4 (0.6)	11 (1.6)	1

Reviewer-created table from ADAE and ADSL for study 303 using FDA-created queries

Table 60 Group 3: TEAEs in the Open-Label Study 201 **(≥2%** of Rimegepant-Treated Patients)

	75 mg N=1798
Dyspepsia, N/V, epigastric pain	104 (5.8)
N/V	77 (4.3)
Abdominal pain, distention	64 (3.6)
Arthralgia, arthritis	55 (3.1)
Somnolence, fatigue, sedation	48 (2.7)
Dizziness	45 (2.5)
Diarrhea	44 (2.4)
Headache	42 (2.3)

Reviewer created table from dataset ADAE from study 201 where APHASE ≠ SCREENING

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Reviewer's comment: The applicant has not proposed a table for the adverse events section. The applicant's proposal for section 6 is to describe the incidence of nausea in rimegepant-treated patients as compared to placebo-treated patients. However, there appears to be a consistent imbalance as compared to placebo in the rates of gastrointestinal adverse events; Because the percentages of patients experiencing these effects is quite low in the controlled portions of the studies, the risk difference is quite low. However, the relative risk for abdominal pain and the FDA-created query containing abdominal pain is quite high (4.5 and 7). Because the percentage of patients experiencing adverse events in the controlled portion is quite low, I suggest that we consider describing relative risk in addition to the risk difference.

8.4.6. Laboratory Findings

The applicant used the CTCAE scale, version 5.0 for the grading of laboratory data.

Mean Change from Baseline Analyses

I reviewed the applicant's analyses for mean changes from baseline for Group 1a (ISS Appendix tables 4.4.1.2D). See Table 51 for individual listings of each laboratory parameter that the applicant tested. I did not detect any clinically meaningful mean changes from baseline compared to placebo in the applicant's analyses for the following: hematology, chemistry, and urinalysis with the exception of creatine kinase (CK).

In Group 1a, there was an increase in the mean change from baseline for rimegepant as compared to placebo at the 7-day post dose measurement. When examining the median changes, there does not appear to be a clinically significant difference. In fact, the median change from baseline is higher for placebo than for rimegepant. It appears that the mean changes from baseline may have been skewed by an outlier value. When this outlier value was removed, the mean changes were nearly identical.

Table 61 Group 1a: Mean Change from Baseline in CK

CK (U/L)	PBO N=1339	75 mg N=1321
Change from baseline		
Mean	12.2	21.2
Median	2.0	0
Min, Max	-705, 3324	-2647, 19795

This table was adapted from ISS Appendix table 4.4.1.2.D

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Analyses Focused on Outliers

There is no imbalance between placebo-treated patients and rimegepant-treated patients in outlier analyses of elevated CK.

Table 62 Potentially Clinically Significant Postbaseline CK Elevations

CK	Placebo N=1340 n(%)	75 mg N=1321 n(%)
Grade 1 or 2	190 (14.2)	205 (15.5)
Grade 3	12 (0.9)	2 (0.2)
Grade 4	2 (0.1)	4 (0.3)

This table was adapted from ISS Appendix table 4.1.1.1D

CK Toxicity Grading:
Grade 1: >ULN up to 2.5xULN
Grade 2: ≥2.5xULN up to 5xULN
Grade 3: >5xULN up to 10xULN
Grade 4: >10xULN

Investigation-Related Adverse Events

In Group 1a, investigation-related AEs were low in the double-blind treatment period with no notable imbalances compared to placebo (Table 63).

Table 63 Group 1a: Investigation-Related AEs in the DBTP

Preferred Term	Placebo N=1782 n(%)	75 mg N=1771 N (%)
AST increased	1 (0.1)	3 (0.2)
ALT increased	2 (0.1)	3 (0.2)
Bicarbonate decreased	1 (0.1)	0
Bilirubin increased	1 (0.1)	2 (0.1)
Chloride decreased	1 (0.1)	0
Cholesterol increased	0	1 (0.1)
CK increased	10 (0.6)	9 (0.5)
Creatine increased	2 (0.1)	2 (0.1)

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Preferred Term	Placebo N=1782 n(%)	75 mg N=1771 N (%)
Glucose increased	1 (0.1)	0
Lactate dehydrogenase increased	1 (0.1)	2 (0.1)
Potassium increased	2 (0.1)	0
Urea increased	0	1 (0.1)
Uric acid increased	1 (0.1)	0
Eosinophil count increased	0	1 (0.1)
GFR decreased	1 (0.1)	5 (0.3)
HCG increased	1 (0.1)	0
Hemoglobin increased	0	1 (0.1)
Hemoglobin urine	0	1 (0.1)
LFT increased	3 (0.2)	2 (0.1)
Neutrophil count increased	1 (0.1)	0
Opiates positive	0	1 (0.1)
Protein urine	0	2 (0.1)
RBC count increased	0	1 (0.1)
RBCs urine positive	1 (0.1)	0
Urinary casts	0	1 (0.1)
Urine analysis abnormal	1 (0.1)	2 (0.1)
Urine cannabinoids increased	1 (0.1)	0
Urine ketone body present	1 (0.1)	0
WBC count increased	1 (0.1)	1 (0.1)
WBC urine positive	1 (0.1)	1 (0.1)

Reviewer created table from ISS dataset ADAE for Group 1a where TRTEMFL=y and AEBODYS=investigations

8.4.7. Vital Signs

Vital signs including body temperature, respiratory rate, supine and standing/sitting blood pressure, orthostatic blood pressure and heart rate were measured according to the schedule of assessments (see Section 6 under Study Design for a summary of the schedule of assessments). I reviewed the applicant's analyses of vital signs. Rimegepant did not appear to have clinically meaningful changes in mean systolic blood pressure, diastolic blood pressure, temperature, respiratory rate, or weight (analyses of mean changes not shown). I reviewed the analyses presented for studies 301, 302, and 303 (Tables 14.5.1 in the respective CSRs) and for study 201 (Table 14.3.3.1 in the respective CSR).

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Potentially Clinically Significant Changes in Vital Signs

The applicant was asked to provide a table with the number and the percentage of patients with at least one post-treatment vital sign measurement meeting any of these criteria:

- Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
- Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
- Heart rate: <60bpm and > 100bpm

The applicant provided this table in the ISS for Group 1a (Table 64) and the CSR for study 201 (Table 65). I did not detect any imbalance between rimegepant and placebo for SBP, DBP, and HR outliers.

Table 64 Group 1a: Outlier Analysis of Blood Pressure and Heart Rate

	Placebo N=1338 n(%)	75 mg N=1326 n(%)
SBP		
<90mmHg	12 (0.9)	14 (1.1)
>140mmHg	62 (4.6)	74 (5.6)
>160mmHg	1 (0.1)	3 (0.2)
DBP		
<50mmHg	4 (0.3)	3 (0.2)
>90mmHg	84 (6.3)	93 (7.0)
>100mmHg	0	7 (0.5)
HR		
<60bpm	89 (6.7)	79 (6.0)
>100bpm	24 (1.8)	13 (1.0)

This table was adapted from the ISS table appendix 5.1.1D. Vital signs noted in this table were taken while sitting

Table 65 Group 3: Outlier Analyses of Blood Pressure and Heart Rate

	75 mg N=1727 n(%)
SBP	
<90mmHg	72 (4.2)
>140mmHg	252 (14.6)
>160mmHg	18 (1.0)
DBP	
<50mmHg	15 (0.9)

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>90mmHg	351 (20.3)
>100mmHg	38 (2.2)
HR	
<60bpm	312 (18.1)
>100bpm	101 (5.8)

Adapted from the CSR for study 201 table 14.3.3.1.1. Vital signs noted in this table were taken while sitting

Vital Signs in Phase 1 Clinical Studies

Study CN170001: Single and Multiple Dose Study

In the SAD, single doses were administered up to 1500 mg (i.e., 75 mg, 150 mg, 300 mg, 600 mg, 900 mg, and 1500 mg). In the MAD, rimegepant was given once daily for 14 days up to a maximum dose of 600 mg (i.e., 75 mg, 150 mg, 300 mg, 450 mg, and 600 mg). No clear pattern for mean changes from baseline in SBP and DBP were noted in the single ascending dose and multiple ascending dose study (Table 66, Table 67, Table 68, and Table 69).

Table 66 CN170001 SAD: Mean Changes from Baseline in SBP in mmHg (supine)

	Placebo N=14	75 mg N=6	150 mg N=6	300 mg N=6
Time in hours				
1	-2.1	4.7	0.5	3.3
2	7.5	5.8	-1	3.8
3	5.2	2.2	2.8	2.7
4	3.7	3.3	-1	5.2
6	0	-3.2	-3.7	2.5
8	1.2	0.3	-2.2	4.7
12	0.3	-3.4	-5.2	-2.5

This table is adapted from the CSR for study CN170001, table S.7.3.2

Table 67 CN170001 SAD: Mean Changes from Baseline in DBP in mmHg (supine)

	Placebo N=14	75 mg N=6	150 mg N=6	300 mg N=6
Time in hours				
1	1.6	1.5	2.3	0
2	4.6	-1.7	0.5	3.8
3	0.7	2.8	-4	1.7
4	1	0.2	-1.7	4.7

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6	1.5	-0.8	-3.7	-3.8
8	-2	-1.2	-2.5	4.8
12	0.3	2.6	-1.7	-0.8

This table is adapted from the CSR for study CN170001, table S.7.3.2

Table 68 CN170001 MAD: Mean Changes from Baseline in SBP in mmHg (Day 14 supine)

	Placebo N=12	75 mg N=6	150 mg N=6	300 mg N=6
Time in hours				
1	6.5	1.8	-3.2	-0.3
2	2.5	4.2	-2.7	-4.2
3	-3.8	-1.2	-3.5	-1.5
4	-2.9	-6.7	-1.3	6.2
6	-2.6	-2.2	-4.5	-5.3
8	-5.2	-2.2	1.3	-4
12	-4.4	-9.5	-0.3	-1.2

This table is adapted from the CSR for study CN170001, table S.7.3.5

Table 69 CN170001 MAD: Mean Changes from Baseline in DBP in mmHg (Day 14 supine)

	Placebo N=12	75 mg N=6	150 mg N=6	300 mg N=6
Time in hours				
1	1	1.2	-3.7	0.2
2	0.3	0.7	4.5	-4.2
3	2.1	-5.2	0.2	1.8
4	2.9	1.5	-2	0.8
6	-0.9	-1	3.2	-1.8
8	-2.1	-2.7	0.2	-0.7
12	-1.1	-4.8	1	0.2

This table is adapted from the CSR for study CN170001, table S.7.3.5

Reviewer's comment: This evaluation adequately captures Tmax for the tablet (1.9 hours) but is somewhat limited for the ODT (Tmax 1.5 hours). The only notable trend in mean changes in SBP was seen in the 300mg dose SAD portion of CN170003. The mean SBP elevated and remained elevated until 12 hours after dosing. However, at the dose planned for marketing (75 mg) there does not appear to be any notable changes from baseline in SBP or DBP.

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8.4.8. Electrocardiograms (ECGs)

The applicant provided summary statistics for the PR interval, QRS complex, the QT, and the QTcF. This included analyses of the mean change from baseline and outlier analyses. I did not detect any clinically significant changes in PR, QRS, or QT intervals or in the analysis of ECG-related AEs.

Mean Changes in ECG Intervals

I reviewed table 14.5.2.1 from the CSR from studies 301, 302, and 303. There were no clinically significant changes from baseline in the mean HR, PR interval, QRS, or QTcF as compared to placebo in the three pivotal studies.

Analyses Focused on Outliers

Table 70 Group 1a: Max QTcF Post-Baseline

QTcB (msec)	Placebo N=789 n(%)	75 mg N=772 n(%)
>450	95 (12.0)	60 (7.8)
>480	5 (0.6)	3 (0.4)
>500	1 (0.1)	0
QTcF (msec)	N=1335	N=1309
>450	18 (1.3)	17 (1.3)
>480	1 (0.1)	1 (0.1)
>500	0	0

This table was adapted from the ISS/SCS Table 24

In Group 3 there was only 1/1784 patients who experienced a QTcF greater than 500msec.

ECG-Related AEs

There was only one ECG-related AE in a placebo-treated patient in Group 1a. There were none in rimegepant-treated patients. There were 4 patients with ECG-related AEs in Group 3: three with T wave inversion, and one with T-wave amplitude decreased.

8.4.9. QT

The applicant conducted a thorough QT (TQT) study which was reviewed by the

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Interdisciplinary Team for QT Studies (QT-IRT). The QT-IRT reviewed the TQT study BHV3000-109. 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."

8.4.10. Immunogenicity

N/A

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Cardiovascular, Cerebrovascular, and Peripheral Vascular Disease

CGRP is a potent vasodilator. For this reason, there is a theoretical cardiovascular safety risk potentially associated with antagonism of the CGRP receptor. This concern is centered around a potential lack of compensatory vasodilatation in the context of ischemia. Plasma CGRP levels have been found to be increased during myocardial infarction and it is thought that these increased levels of CGRP may act as a defense mechanism (Mair et al. 1990).

Migraine has an association with increased risk of vascular disease especially in patients with migraine with aura (Scher et al. 2005). There is some evidence that migraine patients are at increased risk of cardiovascular events (e.g., ischemic heart disease, myocardial infarction) and increased risk of stroke. These epidemiological findings combined with the theoretical risk of CGRP antagonism have made cardiovascular and cerebrovascular safety issues of concern warranting a closer evaluation.

Reviewer's comment: During the review of prior CGRP receptor antagonists, the inclusion of a warning for the theoretical cardiovascular safety risk in patients with major cardiovascular disease was considered by the Division. A consult from the Division of Cardiovascular and Renal Products (DCRP) was obtained to assess whether the available nonclinical literature supported inclusion of this warning in the label. DCRP concluded that there is consensus that CGRP is a potent microvascular vasodilator, but that CGRP is one of multiple redundant control mechanisms regulating blood flow. They concluded that in animal models, loss of vasodilatation from CGRP antagonism does not result in tissue threatening ischemia.

At that time, a meeting with the Medical Policy and Program Review Council (MPPRC) was requested to discuss whether the animal data was compelling enough to include a warning in section 5 describing the theoretical risk of CGRP receptor antagonism in patients with major cardiovascular disease. The animal data was presented to the MPPRC as were details about the mechanism of CGRP. The Council unanimously felt that the animal data was not compelling

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enough to include a warning in section 5 of the label.

Although the theoretical risk was not included in product labeling because of lack of evidence in animal models, I think careful examination of CV safety in humans is still warranted. The clinical trials in migraine patients generally include younger, healthier patients without major cardiovascular disease and the role of chronic antagonism of CGRP is still unclear in patients with major cardiovascular disease.

Some patients in the controlled trials for rimegepant had cardiovascular risk factors such as diabetes, hypertension, cigarette use, hyperlipidemia, or obesity (Table 71). However, the overall prevalence of pre-existing major cardiovascular disease in the entire database was very low. I summarized some of the major cardiovascular, cerebrovascular, and peripheral vascular disease reported in Group 1a (Table 72).

Table 71 Group 1a: Baseline Cardiac Risk Factors

	Placebo N=1782 n (%)	75 mg N=1771 n (%)
Diabetes	63 (3.5)	62 (3.5)
Treatment for hypertension	197 (11.1)	222 (12.5)
Current cigarette use	199 (11.2)	216 (12.2)
Hyperlipidemia*	156 (8.8)	166 (9.4)
BMI≥30 kg/m² **	833 (46.7)	851 (48.1)

Summarized from ISS table 1.3.4D
*Calculated by the reviewer from dataset ADMH where SAFFL=Y, MHDECOD=hyperlipidemia or hypercholesterolemia
**Calculated by the reviewer from dataset ADSL where SAFFL=Y, analysis of BMI≥30 by TRT01A

Table 72 Group 1a: Summary of Major Cardiovascular, Cerebrovascular, or Peripheral Arterial Disease Medical History

	Placebo N=1782 n (%)	75 mg N=1771 n (%)
Angina (pectoris or unstable)*	2 (0.1)	4 (0.2)
Arteriosclerosis (aortic or coronary)*	2 (0.1)	3 (0.2)
Coronary artery disease*	3 (0.2)	7 (0.4)
Myocardial infarction	1 (0.1)	2 (0.1)
Acute coronary syndrome	0	1 (0.1)
Percutaneous coronary intervention	1 (0.1)	1 (0.1)
Coronary artery bypass surgery	1 (0.1)	1 (0.1)

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Cardiomyopathy	0	1 (0.1)
Carotid occlusion	1 (0.1)	0
Mitral valve repair	1 (0.1)	0
Pulmonary embolism/DVT*	8 (0.4)	11 (0.6)
Transposition of the great vessels	0	1 (0.1)
Wolf-Parkinson-White	1 (0.1)	2 (0.1)
Stroke or transient ischemic attack	6 (0.3)	6 (0.3)
Peripheral vascular disease	3 (0.2)	2 (0.1)
Ischemic bowel disease	1 (0.1)	1 (0.1)
Raynaud's phenomenon*	7 (0.4)	4 (0.2)

Summarized from ISS table 1.3.4D; *Calculated by the reviewer from dataset ADMH

I assessed the database for potential cardiovascular, cerebrovascular, and peripheral vascular adverse effects of rimegepant. In the double-blind treatment period (Table 73) and the open-label safety study (Table 74), the incidence rates for AEs related to cardiovascular, cerebrovascular, or peripheral vascular disorders was low with no imbalance as compared to placebo.

Table 73 Group 1a: Summary of Preferred Terms for Cardiovascular, Cerebrovascular, and Peripheral Vascular Disease AEs

Preferred Term	Placebo N=1782	75 mg N=1771
Aphasia	1 (0.1)	0
Cardiomegaly	1 (0.1)	0
Cholesterol increased	0	1 (0.1)
Hypertension/blood pressure increased	6 (0.3)	6 (0.3)
ECG PR shortened	1 (0.1)	0
Hyperlipidemia	1 (0.1)	0
Palpitations	2 (0.1)	0
Syncope	3 (0.2)	0
Tachycardia	4 (0.2)	1 (0.1)

Reviewer created table from dataset ADAE for studies 301, 302, and 303

Table 74 Group 3: Summary of Preferred Terms for Cardiovascular, Cerebrovascular, and Peripheral Vascular Disease AEs

Preferred Term	75 mg N=1798
Angina	1 (0.1
Aortic aneurysm	1 (0.1)

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Aortic dissection	1 (0.1)
Atrial fibrillation	1 (0.1)
AV block first degree	1 (0.1)
Blood cholesterol/lipids/LDL/triglycerides increased	3 (0.2)
Blood pressure increased/hypertension	27 (1.5)
Bradycardia	1 (0.1)
ECG changes (ST segment depression, T wave decreases, T wave inverted)	5 (0.3)
Hemiparesis/hemiplegia	2 (0.1)
Palpitations	11 (0.6)
Presyncope/syncope	4 (0.2)
Sinus tachycardia	1 (0.1)
Supraventricular extrasystoles	1 (0.1)
Ventricular extrasystoles	4 (0.6)
Ventricular tachycardia	1 (0.1)

Reviewer created table from dataset ADAE for study 201

A deficiency in the release of CGRP has been implicated in the lack of vasodilatation observed in Raynaud's phenomenon, and administration of CGRP has been shown to have a beneficial effect (Bunker et al. 1993, and Russell et al. 2014). There were 11 patients in the rimegepant database with a medical history of Raynaud's phenomenon. One of them was noted to have worsening Raynaud's phenomenon that was coded as moderate in severity. The patient did not discontinue from rimegepant and the symptoms eventually resolved.

Reviewer's comment: While not convincing enough to include a statement in product labeling, it may be worth monitoring in the postmarketing setting when more patients with Raynaud's phenomenon may be exposed to rimegepant or develop a Raynaud's-like phenomenon.

Hypertension

There is some suggestion that CGRP has a role in the development of hypertension (Russell et al. 2014) although that understanding is not clear. It may be that CGRP release is enhanced early in the development of hypertension as a compensatory or protective effect.

In Group 1a, there was no imbalance between placebo-treated and rimegepant-treated patients in the incidence of adverse events related to hypertension. In Group 1a there were 6 (0.3%) placebo-treated patients, and 6 (0.3%) patients treated with 75 mg of rimegepant who experienced treatment-emergent adverse events related to hypertension. In Group 3 (open-label study), the overall rate of hypertension-related TEAEs were low. There were 27 (1.5%) of patients treated with 75 mg of rimegepant who experienced hypertension-related TEAEs. All

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cases in the open-label study were coded as mild to moderate in severity. In one case rimegepant was withdrawn. This patient had a prior history of hypertension with a baseline blood pressure of 148/78. Her blood pressure reached a maximum of 158/102 and returned to baseline about 4 weeks after her last dose. In the open-label study, there were 19/27 patients who required treatment for AEs coded as hypertension or elevated blood pressure.

8.5.2. **Hepatoxic Effects**

Because of hepatoxic effects seen in other CGRP antagonists that are no longer in development, the applicant was asked to conduct a dedicated hepatic safety study to assess the hepatotoxicity of rimegepant in patients taking the drug daily or near daily. The applicant did not conduct this study. Instead the applicant attempted to enrich the long-term open-label study 201 with patients who were likely to use rimegepant more frequently. In addition, the applicant included a treatment arm of patients in the open-label study who took rimegepant scheduled every other day regardless of whether the patient had a migraine. Patients in this treatment arm could take additional PRN doses on those days when the patient experienced a migraine. These patients took rimegepant every other day for a total of 12 weeks.

Study 201

In Study 201, there were 286 patients treated with rimegepant every other day (EOD) scheduled with PRN doses for days when the patient experienced a migraine. There was one patient in the PRN dosing group (USUBJID (b) (6)) that had an ALT≥3xULN with a TBili ≥2x ULN. This case did not meet criteria for Hy's Law as the patient had an alternative cause for his elevated ALT and TBili and the elevations did not occur simultaneously. There was also one case in study 201 (USUBJID (b) (6)) that was coded as drug-induced liver injury. This case was likely not related to rimegepant. Both patients were taking medications that are known to be hepatotoxic. Please see section 8.4.2 for more details regarding these cases.

Treatment-emergent hepatic adverse events were low (Table 75). There were no hepatic TEAEs in patients who received rimegepant EOD for 12 weeks. There were no cases of Hy's Law in either treatment group. There were no clinically meaningful post-baseline elevations in AST, ALT, or Tbili for patients treated EOD with rimegepant. A graphical representation (eDISH plot) of post-baseline elevations in ALT, and Tbili can been seen in Figure 3.

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Table 75 Study 201: Hepatic TEAEs

Preferred Term	75 mg (EOD+PRN) N=286 n(%)	75 mg (PRN) N=1498 n(%)
ALT increased	0	9 (0.6)
AST increased	0	7 (0.5)
Bilirubin increased	0	5 (0.3)
GGT increased	0	3 (0.2)
Liver function test increased	0	5 (0.3)
Drug-induced liver injury	0	1 (0.1)
Hepatic cyst	0	1 (0.1)
Hepatitis C	0	1 (0.1)
Hemangioma of liver	0	1 (0.1)

This table was adapted from the CSR for study 201, table 14.2.1.8.1

Table 76 Study 201: Post Baseline Elevations in AST, ALT, and TBili

	75 mg (EOD+PRN) N=286 n(%)	75 mg (PRN) N=1498 n(%)
AST		
≥3x ULN	0	16 (1.1)
≥5x ULN	0	7 (0.5)
≥10x ULN	0	3 (0.2)
ALT		
≥3x ULN	1 (0.3)	16 (1.1)
≥5x ULN	0	8 (0.5)
≥10x ULN	0	1 (0.1)
TBili (mg/dl)		
≥1.5xULN	2 (0.7)	4 (0.3)
≥ 2xULN	0	1 (0.1)

This table was adapted by the reviewer from outputs provided by the JumpStart team.

Reference ID: 4566903

Figure 3 Study 201: eDISH Plot for Post-Baseline Measurements

This figure was taken from the CSR for study 201, figure 14.7.2.1

Studies 301, 302, and 303

Data from the three pivotal studies was pooled to create the tables and eDISH plot in this section (Figure 4). There were 1782 patients who received placebo, and 1771 patients who received rimegepant in the three pooled studies. Hepatic TEAEs including investigation-related AEs were overall low and balanced between placebo and rimegepant in pooled data.

Table 77 Studies 301, 302, and 303: Hepatic TEAEs

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)

This table was adapted from appendix table 3.2.8.1D from the ISS

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Table 78 Studies 301, 302, and 303: Post Baseline Elevations in AST, ALT, and TBili

	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

This table was created by the reviewer by combining JumpStart outputs for studies 301, 302, and 303

Figure 4 Studies 301, 302, 303: eDISH Plot for Post-Baseline Measurements

This figure was taken from the SCS, figure 5. Note: Only patients whose postbaseline labs were obtained within 7 days of dosing are included in this figure provided by the applicant

Reviewer's comment: The applicant had been asked to conduct a dedicated hepatotoxicity study in patients receiving rimegepant daily or near daily to try to address the concern

regarding hepatotoxicity seen in other CGRP receptor antagonists that were previously in development. The applicant did not conduct this study. Instead the applicant attempted to address the concern by enriching the open-label study with more frequent use of rimegepant. The applicant included 286 patients who took rimegepant on a scheduled every other day regimen to capture this more frequent use. The data from the EOD arm of the study looks like there is no evidence of hepatotoxicity with the use of rimegepant 75 mg on an EOD basis.

8.5.3. Gastrointestinal Effects

Nonclinical data suggest that CGRP has protective effects against gastric injury. Mechanisms of gastric protection include inhibition of gastric secretion of somatostatin, stimulation of gastric mucin synthesis, and mucosal hyperemia via direct vasodilation. Endogenous CGRP has been shown to reduce gastric acid secretion. Theoretically concerns with CGRP antagonists include increased risk of gastric ulcer, bowel ischemia, and obstruction as CGRP has known roles in blood flow, inflammation, motility, and secretion into the colon.

There were 8 GI-related SAEs in the open-label study: appendiceal mucocele, ischemic colitis, constipation, diabetic gastroparesis, gastritis, acute pancreatitis, and peritoneal hemorrhage. Several of these SAEs resulted in withdrawal from rimegepant (i.e., constipation, ischemic colitis, and acute pancreatitis) or dosing interruption (appendiceal mucocele, and peritoneal hemorrhage). There was one case of abdominal pain that resulted in drug withdrawal, and one case that resulted in dosing interruption. There were two additional cases of constipation that resulted in withdrawal from rimegepant. In the open-label study, approximately 1.8% of patients reported the AE of constipation.

In the Gastrointestinal Disorders SOC there were 42 (2.4%) placebo-treated patients and 57 (3.2%) rimegepant-treated patients who experienced GI-related AEs. There were 219 (12.2%) patients in the open-label study who experienced GI-related AEs.

Reviewer's comment: Constipation with serious complications has been reported with the use of other CGRP antagonists. There was no imbalance compared to placebo in the rates of development of constipation during the controlled trials; however, there were two cases of constipation and a case of ischemic colitis that resulted in withdrawal from rimegepant. While not convincing enough to include in product labeling, it may be worth monitoring in the postmarketing setting given biological plausibility.

8.5.4. Suicidality Assessment

The applicant utilized the Sheehan Suicidality Tracking Scale (S-STS) to assess patients for suicidality in the pivotal studies (301, 302, and 303) and in the long-term safety study (201). The S-STS was obtained monthly during the long-term safety study. There does not appear to be a signal for suicidal ideation or suicidal behavior.

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There were no suicidality AEs reported in the phase 3 single-dose studies 301, 302, and 303. There were 5 patients in the open-label study who had AEs of suicidal thoughts/ideation. Two of the five patients experienced the suicidal ideation during the follow-up period after completion of the study. The other three patients who experienced suicidal ideation had a history of depression and/or anxiety. No suicide attempts were reported. One of the three patients continued in the study without further suicidal thoughts. The other two patients were discontinued from the study. There were 10 additional patients who had scores other than 0 on the S-STS but were not reported as AEs of suicidal thoughts/ideation by the investigators.

8.5.5. Local Tolerability of the ODT Formulation

There were three clinical pharmacology studies and one clinical efficacy study that utilized the ODT formulation. In studies 110, 112, and 113, a local tolerability assessment in the form of an oral cavity inspection was performed one day prior to dosing, 15 minutes after dosing, and at the conclusion of the study. Alterations in the appearance of the tongue, palate, and buccal mucosa were recorded as an AE. A total of 127 subjects received the ODT formulation in the three clinical pharmacology studies combined. In study 303, 682 patients received the ODT formulation. This section summarizes the adverse events related to local tolerability that were experienced by subjects or patients who received the ODT formulation of rimegepant.

In study 110, there was one subject who reported petechiae of the oral mucosa, and one who reported dry throat. In study 112, there was one subject who reported dry mouth, and one who reported oral herpes (LLT cold sores lip). In study 113, there was one subject who experienced an AE of gingival ulceration approximately 0.5 cm in size on the gum. The ulceration was reported as mild and resolved in under 48 hours. There was one AE of oropharyngeal pain and one of oral herpes (LLT cold sore). In study 303, there were two rimegepant-treated patients who reported AEs of dysgeusia. There was one AE of dry mouth, increased thirst, and oral dysesthesia (of the lips).

Reviewer's comment: There was no evidence of local tolerability issues with the use of the ODT product.

8.6. Safety Analyses by Demographic Subgroups

The database for rimegepant overall has very few SAEs and AEs. Analysis of SAEs by demographic subgroup was not possible as there were too few. I have presented the rates of AEs by sex, age, and race in the ISS from the 90-day safety update. This analysis represents 1798 patients who received at least a single dose of rimegepant 75 mg in study 201. Of these, 1189 (66.1%) reported at least one AE at any time. The rates of AEs by sex, age, and race roughly reflects the rates of AEs in ISS. Some of the race categories have too few patients to

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make any meaningful comparisons or conclusions.

Table 79 Study 201: Rates of AEs by Sex, Age, and Race in Patients Exposed to Rimegepant

	Sex		Age		Race		
	M N=191 n(%)	F N=1607 n(%)	< age 40 N=739 n(%)	≥ age 40 N=1039 n(%)	White N=1474 n(%)	Black N=249 n(%)	Other N=75 n(%)
# of patients experiencing AEs	105 (55.0)	1084 (67.5)	490 (66.3)	699 (67.3)	1007 (68.3)	139 (55.8)	43 (57.3)

*Reviewer created table using ISS dataset for study 201 from 90-day update ADAE, and ADSL as denominator

8.7. Specific Safety Studies/Clinical Trials

N/A

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Overall there were very few malignancies in the database. Seven malignancies were detected during the open-label study. The malignancies reported in rimegepant-treated patients were as follows: basal cell carcinoma (2), breast cancer stage I, invasive ductal breast carcinoma, malignant melanoma, and squamous cell carcinoma of the vulva. At this time, I do not detect a signal for the development of malignancy with the use of rimegepant; however, there were too few malignancies to make any definitive conclusions about the carcinogenicity of rimegepant.

8.8.2. Human Reproduction and Pregnancy

Despite the requirements for contraception, the rimegepant development program had some pregnancies. The data are insufficient to support conclusions on the effect of rimegepant on reproduction and pregnancy.

Pregnant and lactating women were excluded from studies of rimegepant. There were 36 pregnancies reported in the initial filing. Of these 36 pregnancies, 25 were in subjects who received at least 1 dose of rimegepant, and 1 was in the partner of a subject who received rimegepant. There were four pregnancies in placebo-treated patients and 6 pregnancies in subjects who never received IP.

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Table 80 Summary of Pregnancy and Outcomes in Patients Exposed to Rimegepant

Birth Outcome	Maternal Exposure
Full term birth without complications	4
Elective termination	3
Spontaneous abortion	5
Pregnancy ongoing	9
Unknown	4
Total	25

Reviewer created table adapted from the ISS Appendix 8F

8.8.3. Pediatrics and Assessment of Effects on Growth

This section is not applicable to this review. Pediatric patients were not exposed to rimegepant. Patients under age 18 were excluded from all studies.

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

A consult to the controlled substance staff (CSS) was placed when the NDA was received. A filing checklist was provided by Dr. Shalini Bansil. Previous interactions with CSS on this product are dated September 13, 2011; March 7, 2017; and February 28, 2019. During the IND review, CSS did not find any indications of abuse potential in in vitro or in vivo studies. Recommendations were made to the applicant to report abuse-related adverse events throughout clinical development.

In accordance with the Guidance for Industry, "Assessment of Abuse Potential of Drugs," the applicant queried the database for the following abuse-related terms: affective disorder, aggression, confusional state, disorientation, dizziness, drug tolerance, drug withdrawal syndrome, euphoric mood, feeling abnormal, feeling drunk, feeling of relaxation, hallucination, inappropriate affect, mood altered, psychotic disorder, somnolence, substance abuse, substance dependence, substance use, substance-induced mood disorder, substance-induced psychotic disorder, and abnormal thinking. The applicant also included the MedDRA PTs from the SMQs for drug abuse, dependency, and withdrawal. There were a total of 15 (0.8%) rimegepant-treated and 17 (1.0%) placebo-treated patients who experienced at least one potential abuse-related adverse event. In Group 3 (long-term open-label study), there were 101 (5.7%) patients who experienced at least one potential abuse-related adverse event. No signal for abuse-related potential was found (Table 81) in the pooled data from the three pivotal studies or in the long-term safety study (Table 82). Cases of accidental overdose reported in Group 3 were of patients who took two rimegepant tablets in a single calendar day.

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There was one case of intentional overdose in the spouse of a clinical trial patient. The spouse was estimated to have taken 30 tablets of rimegepant 75 mg without known sequelae.

Table 81 Group 1a: Adverse Events Associated with Abuse Potential

Preferred Terms	Placebo N=1782 n(%)	75 mg N=1771 n(%)
Asthenia	0	1 (0.1)
Depersonalization	1 (0.1)	0
Depression	2 (0.1)	1 (0.1)
Disorientation	1 (0.1)	0
Disturbance in attention	0	1 (0.1)
Fatigue	1 (0.1)	3 (0.2)
Feeling abnormal	0	1 (0.1)
Hypoesthesia/sensory disturbance	2 (0.1)	2 (0.1)
Insomnia	1 (0.1)	0
Lethargy/somnolence	6 (0.3)	7 (0.4)
Panic attack	1 (0.1)	0
Sleep terror	1 (0.1)	0
Syncope	2 (0.1)	0

This table was adapted from the SCS appendix table 3.2.9.1D

Table 82 Group 3: Adverse Events Associated with Abuse Potential

Preferred Terms	75 mg N=1784 n(%)
Accidental overdose	4 (0.2)
Amnesia/memory impairment	6 (0.3)
Apathy	1 (0.1)
Asthenia	2 (0.1)
Confusional state	3 (0.2)
Depressed mood/depression	9 (0.5)
Disorientation	1 (0.1)
Disturbance in attention	1 (0.1)
Drug intolerance	1 (0.1)
Fatigue	25 (1.4)
Feeling abnormal	2 (0.1)
Gait disturbance	1 (0.1)

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Hypoesthesia	6 (0.3)
Insomnia/parasomnia	18 (1.0)
Irritability	1 (0.1)
Lethargy/somnolence/sedation	26 (1.5)
Malaise	2 (0.1)
Medication overuse headache	1 (0.1)
Mood swing	1 (0.1)
Panic attack	3 (0.2)
Seasonal affective disorder	2 (0.1)
Syncope	1 (0.1)
Visual perseveration	1 (0.1)

This was adapted from Table 14.2.2.1.2.X3 from the CSR for study 201

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

This section is not applicable. Rimegepant is not marketed in any country at the time of this review.

8.9.2. Expectations on Safety in the Postmarket Setting

The applicant attempted to include a population representative of the U.S. migraine population.

8.9.3. Additional Safety Issues from Other Disciplines

The applicant attempted to include a population representative of the U.S. migraine population. The demographics of the patients included seem to adequately represent the U.S. population. However, the inclusion and exclusion criteria effectively selected for a relatively healthy population. The migraine studies excluded patients with recent cardiovascular disease, and major psychiatric disorders. This may limit the generalizability of the safety data to the larger U.S. population when considering that postmarketing use will be much less restrictive. The applicant attempted to include the over 65 population in this study. Patients in this age bracket in the general population will be expected to have higher rates of cardiovascular disease than those who were included in the pivotal studies, but the number of patients enrolled in the studies was quite small.

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8.10. Integrated Assessment of Safety

The following safety issues were examined in this review based on the theoretical concerns associated with CGRP antagonism: cardiovascular, cerebrovascular, peripheral vascular, and gastrointestinal. Close attention was also paid to hepatoxicity given the prior history with small molecular CGRP receptor antagonists that were previously in development. The safety of rimegepant has been evaluated in three large double-blind placebo-controlled studies and a large open-label study. My review of these trials has not revealed a clear relationship to any serious safety issues related to the use of rimegepant.

The review focusing on cardiovascular and cerebrovascular disorders did not reveal any potential safety concerns in regard to toxicity associated with the use of rimegepant. However, this review is extremely limited as the population studied was primarily healthy. The applicant included some patients over the age of 65 in the studies; however, the overall presence of cardiovascular, cerebrovascular, and peripheral vascular disease was quite low.

Another safety concern for the review was gastrointestinal toxicity. The primary finding was an increase in nausea with the use of rimegepant. No one discontinued due to nausea. There was one patient who experienced ischemic colitis and one patient who experienced colonic inertia leading to bowel resection. Neither case was clearly caused by the use of rimegepant. However, given the biological plausibility of the role of CGRP antagonism in ischemia and bowel motility, it is something that may need monitoring in the postmarketing setting.

Another safety concern addressed in this review is the concern for hepatotoxicity. There were no cases of Hy's law identified during the review in the three phase 3 pivotal studies or open-label study. The applicant enriched the long-term safety study to evaluate hepatotoxicity in frequent users of rimegepant 75 mg. There was no evidence of hepatoxicity from the use of rimegepant 75 mg every other day over a 12-week period.

There are still many uncertainties that remain with the use of rimegepant that may arise in the postmarketing period and will need to be monitored carefully. Theoretical concerns related to the cardiovascular risk of rimegepant remain. Patients with major cardiovascular disease were effectively excluded from clinical studies. The theoretical risk of CGRP antagonism lies with the potential loss of compensatory vasodilatation in the setting of ischemia. There is no data yet on the consequence of chronic CGRP antagonism in patients with cardiovascular disease. Other drugs that have been approved in this class, despite not being labeled with cardiovascular risk language, are conducting enhanced pharmacovigilance in the postmarketing setting for myocardial infarction, and stroke. I recommend that this should be done for rimegepant as well.

Another concern for rimegepant that is unique to medications that are used for the acute

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treatment of migraine is the development of medication overuse (MO). This phenomenon is described in product labeling for all triptans and NSAIDs that are approved for the acute treatment of migraine. If used daily and consistently, CGRP receptor antagonists may be useful for the preventive treatment of migraine. However, thus far there is no data to support or refute whether the use of short-acting CGRP receptor antagonists can lead to the development of medication overuse when used on an intermittent basis. My concern is that the way drugs are used for the acute treatment of migraine is important for the development of MO rather than the mechanism by which the drug acts as this phenomenon is seen in drugs that act across a variety of mechanisms. A class warning was not added to the label of the recently approved ubrogepant and will not be added to the label of rimegepant. However, whether intermittent use of CGRP antagonists can lead to medication overuse remains to be seen.

9. Advisory Committee Meeting and Other External Consultations

An advisory committee meeting is not anticipated for this product.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The final label was not available at the time of this review. After reviewing the applicant's submitted application, I have the following recommendations for labeling:

Section 2: I recommend removal of the following phrase (b) (4) I recommended stating that the safety of treating more than 15 migraines per month in a 30-day period has not been established.

Section 14: I recommend including a graph of the co-primary endpoints. I propose the following tables for the efficacy section of the product label:

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Table 83 Migraine Primary Efficacy Endpoints for Studies 301, 302, 303

	301		302		303	
	75 mg	PBO	75 mg	PBO	75 mg	PBO
Pain Freedom at 2 hours						
n/N	104/543	77/541	105/537	64/535	142/669	74/682
%Responders	19.2	14.2	19.6	12.0	21.2	10.9
Difference from placebo	5.0		7.6		10.3	
p-value		0.0298		<0.001		<0.001
Freedom from MBS						
n/N	199/354	150/541	202/537	135/535	235/669	183/682
%Responders	36.6	27.7	37.6	25.2	35.1	26.8
Difference from placebo	8.9		12.4		8.3	
p-value		0.0016		<0.001		0.001

Table 84 Migraine Secondary Efficacy Endpoints for Study 303

	75 mg	PBO
Pain Relief at 2 hours		
n/N	397/669	298/682
% Responders	59.3	43.3
Difference from placebo	16.0	
p-value		<0.001
Sustained Pain Freedom at 24 hours		
n/N	105/669	38/682
% Responders	15.7	5.6
Difference from placebo	10.1	
p-value		<0.001
Use of Rescue Medication		
n/ N	95/669	199/682
% Responders	14.2	29.2
Difference from placebo	-15.0	
p-value		<0.001
Functional Disability at 2 hours		
n/N	255/669	176/682
% Responders	59.3	43.3
Difference from placebo	16.0	
p-value		<0.001

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10.2. Nonprescription Drug Labeling

N/A

11. Risk Evaluation and Mitigation Strategies (REMS)

N/A

12. Postmarketing Requirements and Commitments

PMRs

1. Deferred pediatric studies required under the Pediatric Research Equity Act
2. Pregnancy registry and outcomes study

Enhanced Pharmacovigilance

1. Myocardial infarction
2. Stroke

13. Appendices

13.1. References

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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 301, 302, 303

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 115		

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Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): none		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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/s/

LAURA A JAWIDZIK
02/26/2020 02:06:00 PM

HEATHER D FITTER
02/26/2020 02:24:22 PM